

ELECTROPHYSIOLOGICAL AND HISTOLOGICAL MAPPING
OF THE CORTICAL AREA OF CENTRAL VISION IN THE DOG

By
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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1993

ACKNOWLEDGEMENTS

I would like to express my sincere thanks and appreciation to everyone who has helped me complete this project. Special thanks go to Dr. William W. Dawson for his support and guidance during these past 4 years. Many thanks go to Dr. Don A. Samuelson for his support and encouragement. Special thanks go to Dr. Kirk N. Gelatt for his contribution of the Beagle dogs for this study, and to Drs. Dennis E. Brooks and Mark B. Sherwood for their advice and support.

I would like to express my sincere gratefulness to Ms. Kim Foli and Minnie Hawthorne for their help in conducting the experiments. Thanks go to Dr. R. Reep, Ms. Patricia Lewis, Heidi Wearne, Aga Agnajelski and Mae Chisholm for their help with the histological studies. Many thanks go to Dr. A. Webb for his help with the anesthesia protocol, and to Dr. S. McGorray for her help with the statistical analysis of the data. I am also grateful to Mr. M. Freeland for his help with the electronic equipment and Ms. Joanne Clarke for all of her help.

Last, but not least, I would like to thank my wife, Iris, for her support, encouragement and understanding that made it all possible.

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KEY TO ABBREVIATIONS

AMF--areal magnification factor
ANOVA--analysis of variance
BAEP--brainstem auditory evoked potentials
cpd--cycles per degree
c.v.--cresyl violet
D--diopter
EPSP--excitatory post synaptic potential
FERG--flash electroretinogram
FVEP--flash visual evoked potentials
IAP--interaural plane
IPSP--inhibitory post synaptic potential
LGN--lateral geniculate nucleus
PERG--pattern electroretinogram
POAG--primary open angle glaucoma
PVEP--pattern visual evoked potentials
RMS--root mean square
V I--visual area I
V II--visual area II
V III--visual area III
VEP--Visual Evoked Potentials

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Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

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December, 1993

Chairperson: Dr. D. A. Samuelson
Major Department: Veterinary Medicine

The visual cortex has been mapped in more than a dozen animal species to date. However, most of the species in which such mapping has been conducted are rodents or nonhuman primates. With the exception of the cat, and possibly the sheep, these animals are rarely presented as patients in veterinary clinics. The visual cortex has yet to be mapped in the dog, the species most frequently seen by veterinarians. This gap in our understanding of the canine has hampered clinicians and surgeons attempting to diagnose and treat neurological and ophthalmological disorders in the dog. It has also greatly complicated the work of researchers performing electrophysiological experiments in the canine visual system, and severely limited the use of the dog as a model for ophthalmological and neurological disorders.

The aim of this study was to map the area of central vision in the canine cortex. After surgically exposing the cortical surface, the dog was paralyzed and its retinal area centralis stimulated by a pattern of alternating bars. An electrode mounted on a stereotaxic device was used to perform a search grid and record the resulting electrical signals from the cortical surface. Histological studies were conducted to confirm the cytoarchitecture and myeloarchitecture of the recording site, and correlate them to the electrophysiological findings.

Based on the results of these studies, it was determined that the primary cortical area of central vision in dogs lies at the junction of the marginal and endomarginal sulci. The stereotaxic coordinates of this region in the Beagle are 11.3 ± 0.4 mm anterior to the interaural line and 8.3 ± 0.1 mm lateral to the midline. In Greyhounds the respective figures are 15.6 ± 0.1 and 8.5 ± 0.6 . A significant difference in the location of the cortical area of central vision between the two breeds was found only along the anterior-posterior axis ($p \leq 0.04$). No significant differences in the location of the cortical area of central vision were found between normal and glaucomatous Beagles ($p > 0.53$). There was a high degree of correlation ($\alpha = 5\%$) between the electrophysiological and histological locations of the area of central vision. The possible implications for comparative electrophysiological and anatomical research are discussed.

CHAPTER 1 INTRODUCTION

Location of the Primary Visual Cortex

Mapping of the visual cortex in man was first performed by Holmes (1) in World War I, using wounded British soldiers who suffered brain injuries. The first animal whose visual cortex was mapped was the cat, which was studied by Talbot in 1940 (2). Since then, mapping of the visual cortex has been carried out in the owl monkey (3), squirrel monkey (4), macaque monkey (5) and bushbaby (6). Nonprimates whose visual areas have been mapped include the tree shrew (7), rabbit (8), guinea pig (9), sheep (10), rat (11), mouse (12), hedgehog (13), marmoset (14), degu (15), golden hamster (16) and grey squirrel (17).

The early works performed on the visual cortex in man and cat revealed that the primary visual area, so called because it is the main recipient of lateral geniculate nucleus (LGN) input, occupies the region known as Brodmann's area 17 (1, 2). This area is a histologically defined region in the occipital lobe, possessing unique cytoarchitectural and myeloarchitectural characteristics, the boundaries of which were determined for humans in the early 20th century (18). In man, this area lies on the medial aspect of the occipital

lobe, along the banks of the calcarine sulcus, bounded anteriorly by the cuneate sulcus and posteriorly by the collateral sulcus (19). In the cat, it occupies the posterior-medial portion of the cortex, extending from the crown of the lateral gyrus on the dorsal surface to the superior bank of the splenial sulcus on the medial surface (20). This area has also been called the striate cortex, due to the large concentration of heavily myelinated fibers in layer IV, or V I (Visual I), a physiological term coined by Woolsey and Fairman in 1946 (21). It should be noted that a significant degree of individual variability has been shown in the location of the striate cortex in man (22). However, modern magnetic resonance imaging techniques show no zonal variation in the patterns of the cuneate and collateral sulci of the medial occipital lobe in man (23). In standard human ophthalmology texts the cuneate and collateral sulci are still referred to as the borders of area 17 (19).

A second visual area, known as V II, was discovered by Talbot in 1942, while working on the cat (24). Since this area lies as a concentric ring lateral to the striate cortex, it is also called the parastriate cortex (25). In all mammalian species studied to date, this region corresponds histologically to Brodmann's area 18, which is adjacent to Brodmann's area 17 (26).

Since Talbot's discovery of a second visual area in the cat, multiple visual areas have been discovered in almost

every species studied. In the cat, V III occupies Brodmann's area 19, and since it is also shaped as an outer concentric ring surrounding V I and V II, it has also been called the peristriate cortex (25). Together, these three visual areas occupy most of the feline occipital lobe (26). Additional visual areas have been discovered in the Clare-Bishop area of the feline cortex (27), while in man it has been shown that visual processing takes place as far away as the temporal and parietal lobes (28). Together with V II these multiple visual areas are known collectively as the extrastriate visual cortex (26).

The existence of these multiple cortical visual areas reflects the extent of the development of the mammalian visual system. For example, three cortical visual areas have been identified in the hedgehog, a primitive insectivore (13). Four such areas have been located in the mouse (29). In the cat, on the other hand, a dozen extrastriate visual areas, mostly lying lateral to V I, have been identified (30). These areas differ in their size, neural organization, region of the visual field which they map, and the type of information processed in them. It should also be noted that the mammalian sensory and auditory organs also have multiple cortical representations of their stimuli (31). However, since in all species studied to date the projection of the fovea or area centralis lies on the border of areas 17 and 18, this discussion is limited to the description of V I and V II.

Organization of the Visual Cortex

Despite recent advances, V I and V II still remain the most thoroughly investigated visual areas. Since the area of central vision is projected onto their common border, they constitute the focus of interest of this study. There are numerous physiological differences in the representations and processing carried out by these two areas.

Incoming Signal

V I receives its input from the LGN (32, 33). More specifically, these thalamic afferents synapse in layer IVc of V I (19). This input consists of the entire contralateral visual hemifield (20). In some species, including the cat, the input also contains part of the ipsilateral hemifield near the vertical meridian (20). On the other hand V II receives most of its input from V I (32, 34). This input doesn't include the temporal periphery of the visual field; therefore, a smaller portion of the visual field is represented in V II (26).

Representation of the Visual Field

The vertical meridian is represented at the lateral border of V I (20), which in primates lies along the banks of the lunate sulcus (35). The area of central vision is represented at the center of the vertical meridian. Medial movement (i.e., away from the lunate sulcus) on the surface of

the striate cortex represents peripheral movement (i.e., away from the area centralis) in the visual field (20, 26). On the surface of V I, adjacent loci of the cortex map onto adjacent loci of the contralateral visual field (36) in a simple, point-to-point manner. This phenomenon is called a 1st order transformation (37), and has been found in all species studied to date.

In non-primates V II lies laterally to V I (it is antero-lateral to V I in primates), bordering it along the vertical meridian (38). In lower mammals, V II's organization is a mirror image of V I (7, 13, 17). Therefore, movement from V I into V II across the vertical meridian would cause a reversal in the topographic arrangement of the receptive fields. In higher mammals, V II also borders V I along the vertical meridian (Figure 1), but the organization is more complex. Here, adjacent loci in the visual field project onto non-adjacent cortical loci (39). The horizontal meridian serves as the dividing line along which adjacent visual field loci are split. This organization has been called a 2nd order transformation (37). A further complication in the mapping of V II's surface is the existence of regions of topographical irregularity, which defy the normal point-to-point mapping of the visual field (26). This phenomenon has been described both in primates and non-primates (39).

Figure 1.

Representation of the visual hemifield on the cat cortex.

A) Perimeter chart showing the extent of the visual hemifield. Azimuths are illustrated by solid lines and elevations are illustrated by dashed lines. (★)-representation of the area centralis.

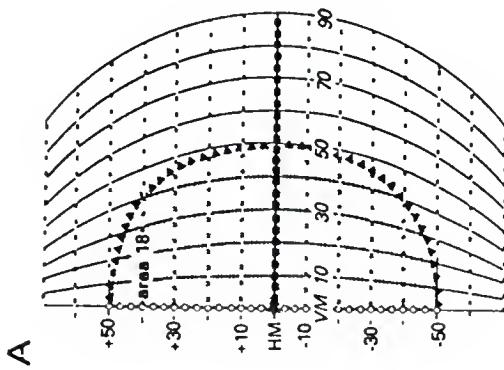
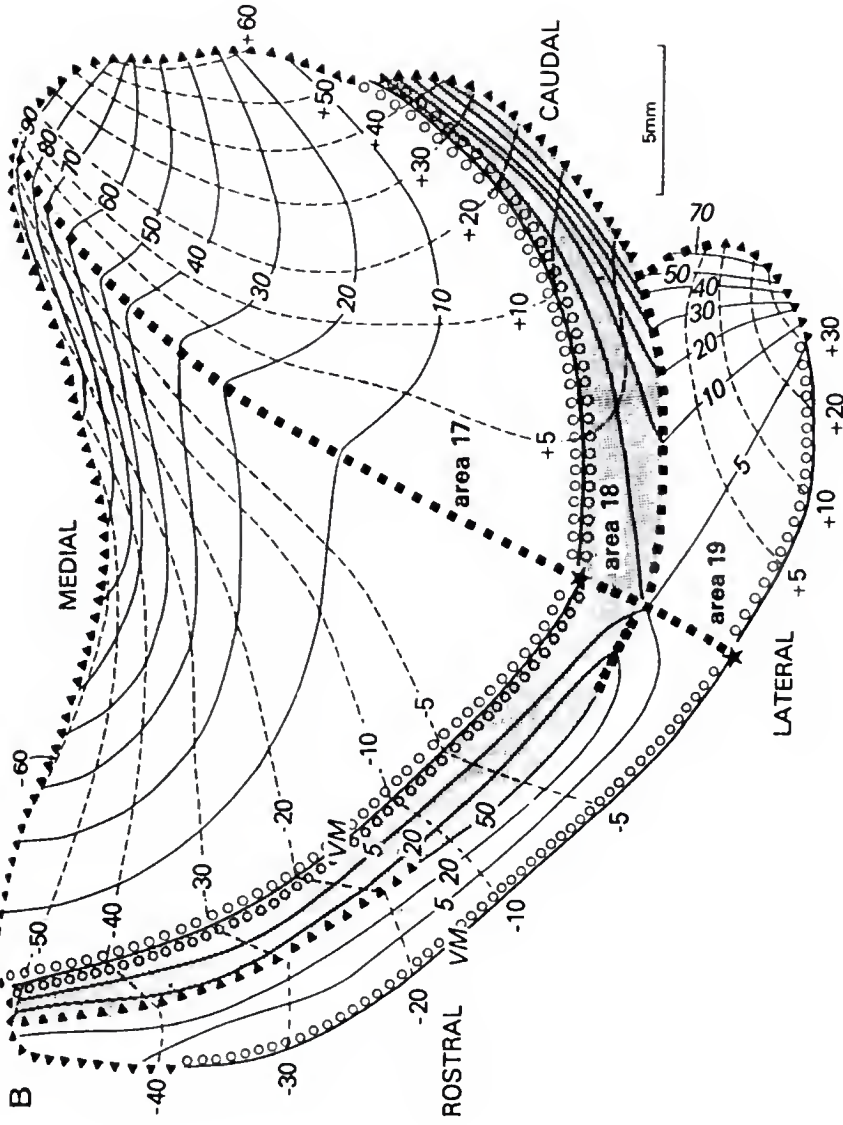
(O)-representation of the vertical meridian.

(■)-representation of the horizontal meridian.

Filled triangles represent the most peripheral part of the visual hemifield.

B) Schematic representation of the visual hemifield in areas 17 (V I), 18 (V II) and 19 of the unfolded cat cortex. Areas 17 and 18 border each other along the vertical meridian. The area centralis is represented at the intersection of the border and of the horizontal meridian representation.

From: Tusa RJ, Rosenquist AC, Palmer LA. Retinotopic organization of areas 18 and 19 in the cat. J Comp Neurol 1979; 185; 657-678 (ref #39).



Area Size and Magnification Factor

The magnification factor is a term coined in 1961 (35) to quantify the disproportionate amount of cortical area devoted to processing visual information from the area centralis. In the retina, the area centralis is defined by the increased density of the ganglion cell and photoreceptor (depending on the species) population. In the cortex, on the other hand, an identical cellular organization serves to represent both the area centralis and the peripheral visual fields (32). The increased detail with which the visual input from the area centralis is analyzed is not a result of thicker layers and increased cell density, as in the retina. Rather, this increased cortical visual discrimination is a result of the increased cortical area devoted to representing the area centralis. In the hedgehog, for example, the surface area of the striate cortex is 20 mm^2 , 50% of which is devoted to representing the central 35° of the contralateral visual hemifield (13). In the cat, the respective figures are 380 mm^2 , 50% of which is devoted to the central 20° of the visual field (20).

The areal magnification factor (AMF) is measured in mm^2 of cortical area devoted to each degree² of the visual field. When a spherical polar coordinate system is used to describe the topography of the visual field, the visual direction relative to the center of gaze is expressed by two angles, azimuth and elevation (20). Thus the shaded area in Figure 1a

represents a visual field $5,000 \text{ degree}^2$ in size (100° along the vertical axis times 50° along the horizontal axis).

The AMF for the cortical representation of the feline area centralis in V I is 3.6 mm^2 of cortex/degree² of visual field (20). In V II, the magnification is usually much smaller. In the cat, the AMF for the representation of the area centralis in V II is $0.75 \text{ mm}^2/\text{degree}^2$ (39), or less than 20% of the AMF value for V I. Since the peripheral 40° of the visual field are not represented at all in V II, it can be said that this region is an extreme example of $\text{AMF}=0 \text{ mm}^2/\text{degree}^2$ (39).

An obvious implication of the difference in AMF values for V I and V II is that these areas differ in size. If V I represents more of the visual hemifield at a greater magnification, it stands to reason that it will be larger than V II or any other visual area (Figure 1). Indeed, V I is usually described as a core, and V II as its adjoining belt (26). Since this belt is narrow, it should be noted that in V II the vertically oriented meridians are much longer than the horizontally oriented ones (39).

Projection of the Area Centralis

As stated previously, the representations of the visual field in V I and V II border each other along the vertical meridian (Figure 1). The area centralis or fovea lies, by definition, in the center of the vertical meridian. In other

words, the representation of the area centralis is on the line demarcating the border between V I and V II (38, 39, 40). This characteristic location has been found in all mammals studied to date, including the rat (11), hedgehog (13), grey squirrel (17), tree shrew (7), rabbit (8), domestic cat (20, 38, 39) and various nonhuman primates (3, 4, 26). In all of these species, the representation of the area centralis invariably lies on the vertical meridian, at the lateral border of V I, next to V II. The fact that this principle holds true in such distantly related mammalian species, but not, for example, in the turtle, makes it reasonable to assume that this trait originates with a common ancestor of all eutherian mammals (13).

The stereotaxic coordinates of the representation of the area centralis in the feline cortex are P3-L5, i.e., 3 mm posterior to the interaural plane (IAP) and 5 mm lateral to the midline (Figure 2) (40). Anatomically, it is located on the crown of the lateral gyrus, near the junction of the lateral and posterior lateral gyri (20).

Number of Maps

As stated earlier, the extent of a species' visual resolution and evolution is reflected not only in the surface area of the striate cortex and the AMF, but also in the number of visually responsive areas of that species (26, 41). In the cat areas 17, 18 and 19 (which borders area 18 along the

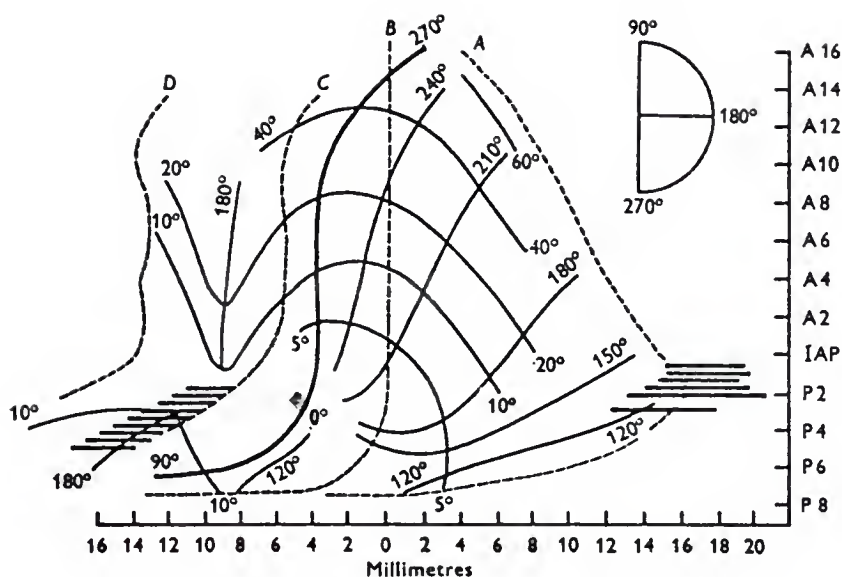


Figure 2. A stereotaxic map of the visual areas in the cat. The heavy line (270° - 90°) is the vertical meridian of the visual field and separates V I medially from V II laterally. The 180° meridian between C and D separates V II from V III. 0° marks the location of the area centralis. Heavy lines indicate areas in which folding of cortex made reliable representation of the cortical surface impossible.

(A) the bottom of the splenial sulcus. (B) the medial edge of the left hemisphere. (C) the bottom of the post-lateral sulcus. (D) the bottom of the lateral sulcus.

Y axis-the anterior-posterior axis, where IAP marks the division between the anterior and posterior planes.

X axis-the medial-lateral axis, where 0 marks the division between the medial and lateral planes.

From: Bilge M, Bingle A, Seneviratne KN, Whitteridge D. A map of the visual cortex in the cat. *J Physiol (Lond)* 1967; 191; 116-118P (ref #40).

horizontal meridian) (42) each contain one representation of the visual hemifield, but the picture is more complicated in other areas. Areas 20 and 21 in the cat each contain two representations of the visual field (43). The lateral suprasylvian region in the cat contains six retinotopically organized units (27, 30). Based on many behavioral studies in nonhuman primates, it is assumed that these extra-occipital areas deal with "higher" visual processing, such as shape and location discrimination and facial recognition (28, 44, 45). It is hoped that once the central canine visual cortex has been accurately localized, future investigation of these "higher" visual processing areas will be attempted in the dog.

Histology of the Visual Cortex

Architectonics of the Cerebral Cortex

Ever since the ground-breaking studies by Brodmann in 1905 and by C. Vogt and O. Vogt in 1919, it has been customary to describe the structure of the cerebral cortex in architectonic, rather than histological, terms (18, 46). In other words, local variations in the array, numbers and gross form of the cells forming the individual cortical layers, rather than a specialized cell type, characterize the various cortical regions of the brain (46). Architectonically, there are two ways to describe the structure of the cerebral cortex: (1) cytoarchitecture, referring to cell bodies stained by Nissl stains, and (2) myeloarchitecture, referring to

variations in fiber myelination as revealed by myelin stains (47). Later works used electrophysiological methods to determine the correlation between Brodmann's architectonic divisions (18) and the physiological functions of these areas (2, 21, 24). These methods revealed a remarkable correlation between the early histological and the more recent physiological maps of the cortex. As stated previously, the architectonically defined areas 17, 18 and 19 correspond precisely with the physiologically defined visual areas V I, V II and V III, respectively.

Cytoarchitecturally, several types of cells can be found in the cerebral cortex. Stellate, also known as multipolar or granular, cells function as cortical intraneurons (48). Morphologically they can be divided into fusiform cells (which are vertically oriented) and basket cells (which are horizontally oriented). These cells have either spinous or non-spinous dendrites, which extend into adjacent layers, as do their axons (19). Pyramidal cells, on the other hand, project out of the cortex, to the white matter or subcortex (19). As the name implies, they are shaped like a pyramid, with one apical dendrite, several basal dendrites extending from the lower angles and an axon continuous with its base (19). Generally speaking, pyramidal cells are typical of motor regions of the cortex, while granular cells dominate in the sensory areas (19). Myeloarchitecturally, two types of fibers can be found in the cerebral cortex: horizontal fibers

connecting various regions and layers of the cortex, and vertical fibers which are mostly thalamic afferent fibers (19).

In 1905, working with eight mammalian orders and using cytoarchitectural methods, Brodmann divided the cerebral cortex into 6 layers, or laminae (18). Ten years later, using myeloarchitectural methods, Vogt and Vogt arrived at a similar conclusion (46). Furthermore, Brodmann's and Vogt's divisions overlapped to a great extent, proving that either method is adequate to describe the cortical architecture (46). Based on their findings, the 6 layers can be described as follows (18, 19, 46, 47, 48):

Layer I. This outermost layer has been called the plexiform, molecular or zonal layer. Cytoarchitecturally, this is a cell-poor layer in the adult, though during fetal development it is populated by superficial granular cells (49). Only few small stellate cells possessing wide horizontally spreading axons are to be found in this layer after birth. Myeloarchitecturally, the layer contains a relatively small amount of tangential nerve fibers.

Layer II. The external granular layer contains small, dense pyramidal cells, characterized by apical and basal dendrites spreading more or less directly into the adjacent layers. Few stellate cells may also be found in this layer. Myeloarchitecturally this layer is the poorest in horizontal

fibers, and has therefore also been called the dysfibrous layer.

Layer III. The external pyramidal layer is populated by pyramidal cells, characterized by a graded increase in their size, i.e., medium size cells near layer II and larger cells near layer IV. The apical dendrites of these cells reach layer I, while their basal dendrites reach layer IV. Their axons descend all the way into the white matter. Myeloarchitecturally layer III shows an increasing amount of horizontal fibers, corresponding to the increasing gradient of cells size.

Layer IV. The internal granular layer is populated mainly by small stellate cells, characterized by a starlike pattern of spineless dendrites. This layer has rather well demarcated borders with layers III and V, and its width and cell density form the main criterion for differentiating between the different cortical areas. Myeloarchitecturally this layer contains the outer stripe of Baillarger, also called the stria of Gennari, formed by the large number of fibers which terminate and synapse here.

Layer V. Called the ganglionic or inner pyramidal layer. This layer is populated by large pyramidal cells, the axons of which descend into the white matter as far down as the spinal cord. This layer has been sub-divided by Brodmann into layer Va, which contains larger pyramidal cells, and layer Vb, containing medium size cells. Ramon and Cajal went as far as

counting these subdivisions as two individual layers (50). Myeloarchitecturally, layer V had been called the interstriate layer, since it contains less horizontal fibers than the two adjacent stripes of Baillarger.

Layer VI. This innermost layer has been called the multi-form or spindle cell layer. As the first name implies, this layer is populated by an assortment of spindle, pyramidal and stellate cells which gradually thin out towards the white matter. Myeloarchitecturally this layer contains an opposing gradient of an increasing number of horizontal fibers which eventually fuse with the white matter.

Distinguishing Features of the Striate and Parastriate Cortex

Area 17 in the cat is characterized by an unusually thin layer II, which is almost indistinguishable from layer III (48). In humans layer II is essentially similar to that of the cat, although layer III in humans is populated by a somewhat greater concentration of pyramidal and stellate cells (19).

However, as stated previously, the characteristic features of area 17 are to be found mainly in layer IV and the other deep layers. As is the case with all other sensory cortical areas, area 17 contains a large number of granular cells. This is especially true of layer IV, where the cells are densely packed, and which is wider in area 17 than in any other cortical region (19). Another unique aspect of area 17 is the prominence of the outer stripe of Baillarger, which in

fact is almost visible to the naked eye (19). It should be noted that in primates an inner stripe of Baillarger, located throughout layer VI of area 17 in most mammals, is present only near the border with area 18 (47).

In his original work, Brodmann divided lamina IV of area 17 into three sublayers, the outer two of which contain large numbers of myelinated fibers (18), and therefore form the true outer stripe of Baillarger (47). Layers IVa and IVb are populated by large stellate and fusiform cells, with which cortical inter-connecting (association) axons synapse (48). Layer IVc is populated mainly by small stellate cells, and it is here that thalamic afferents from the LGN synapse (19). Layer V is thin and sparsely populated by large pyramidal cells (47). It therefore contrasts sharply with the two adjacent layers which contain large numbers of cells and myelinated fibers.

Area 18, which forms a concentric ring lateral to area 17, differs markedly from the striate cortex in both its myeloarchitecture and cytoarchitecture. Layer III of the parastriate cortex is populated by large pyramidal cells and contains many coarse, obliquely oriented fibers (42, 47). Therefore, as opposed to area 17, this results in a wide and prominent layer III, quite distinct from layer II (20). In fact it is so wide that sometimes it is divided into two sub-layers (48). Layer V is also more prominent in area 18, containing fewer large cells (48), but possessing a large

concentration of radially oriented fibers (20, 39). The fibers in layer IV of area 18 are also radially oriented, as opposed to the horizontal and vertical orientation in area 17, thus making for a prominently myelinated band in layers IV and V (20, 39). On the other hand, layer VI of area 18 is narrower and has a more sparse cell population than that of area 17 (20). It also contains fewer fibers than the striate cortex (39). This, coupled with the fact that layer V displays prominent myelination, makes for a wider myelinated zone in area 18, one in which the inner stripe of Baillarger is virtually indistinguishable from the outer stripe (39, 47, 48).

Visually Evoked Potentials

The visually evoked potential (VEP) is an electrical signal produced by the visual centers of the cortex as a result of retinal stimulation.

VEP's in the Normal Dog

In undilated and non-anesthetized dogs, flashes of white light elicit a signal containing a total of three positive and two negative peaks: P1, N1, P2, N2 and P3 (51). The first VEP in the dog can be recorded 2 days after birth (52). Peak latencies reach maturity at age 11 (for P1) to 38 (for N1 and P2) days (53). All peak-to-peak amplitude measurements reach mature levels 58 days after birth (53). This development

roughly parallels the maturation of the canine ERG. A primitive ERG can be recorded in dogs at age 3 weeks, and by 8 weeks of age the canine ERG is fully developed (54).

In clinically normal, nonsedated dogs, the mean latencies of these five peaks are 14.3, 29.2, 54.5, 78.0 and 98.1 msec, respectively (51). Of the five peaks, P2 is usually the most prominent. Mean amplitudes for P1-N1, N1-P2, P2-N2 and N2-P3 are 7.19, 13.30, 6.13 and 5.88 μ V, respectively (51). In an earlier study, using dogs anesthetized with methoxyflurane, only P2 was identified, but its latency and amplitude were similar to those reported above (55).

Flash VEP vs. Pattern VEP

Generally speaking, two types of light stimuli can be used to elicit visual potentials. Flash VEP (FVEP) is the result of a high intensity, short duration flash of unpatterned light. A patterned stimuli, using checkerboards, gratings, dots or other shapes, can also be used to elicit a visual response. In this study, a pattern reversal stimulus was used, in which a field of vertical dark and light gratings is alternated with its complementary field thus maintaining a constant luminance and eliciting a pattern VEP (PVEP).

As might be anticipated, there are significant differences between the waveforms generated by such different stimuli (Figure 3). The two most significant differences between the two waveforms are the absence of P3 in PVEP, and

the fact that the first peak in PVEP's is negative rather than positive (56, 57). However, it is difficult to describe a "typical" PVEP, because the waveform varies greatly with the luminance, reversal rate, size and location of the stimulated area, and other parameters. In the rat, the peak-to-peak amplitudes of the FVEP are 128 μ V for P1N1, 190 for N1P2, 158 for P2N2, 140 for N2P3 and 165 μ V for P3N3 (56). The values for the rat PVEP are 27 μ V for N1P1, 39 for P1N2, 2.3 for N2P2 and 25 μ V for P2N3 (56). The latencies of the 6 FVEP peaks in the rat are approximately 25, 33, 48, 70, 100 and 165 msec., respectively (56). The latencies of the 5 PVEP peaks are approximately 45, 67, 85, 87 and 112 msec, respectively (56).

Generally speaking, when stimulating the same retinal areas, the FVEP has a different and wider distribution over the scalp when compared to the PVEP (59). However, closer analysis of the various peaks in the rat VEP reveals that the P1, N2 and N3 peaks of FVEP, and the P1 and N3 peaks of the PVEP have a smaller surface distribution of maximal amplitude, indicating, perhaps, a more localized site of origin (56). In human PVEP the 5 peaks are identified as N75, P100, N100, N150 and P200, based on their mean latencies (60).

It has already been established that flash ERG (FERG) and pattern ERG (PERG) have different origins in the retina. The pattern ERG is considered to be an indicator of inner retinal function, while FERG is regarded as an indicator of outer retinal function (61). Separate origins have also been

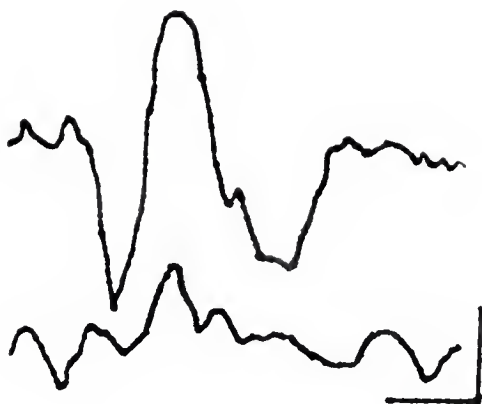


Figure 3. VEP recordings in man

Top-PVEP recordings elicited by 15' checks, 12° in diameter.

Bottom-FVEP recordings elicited by a flash stimulus in the same subject. Luminance and field size were identical to those of the pattern stimulus. N1 is prominent in the FVEP signal but reduced in the PVEP signal. On the other hand, the N2-P2 amplitude is much larger in the PVEP signal. Vertical line: 10 μ V; horizontal line: 100msec.

From: Sokol S. Visually evoked potentials: Theory, techniques and clinical applications. Surv Ophthalmol 1976; 21; 18-42 (ref #58).

suggested for FVEP and PVEP. Differences between FVEP and PVEP in people suffering from optic neuritis have led researchers to conclude that the 2 types of VEP are transmitted by completely separate fibers as early as the optic nerve (62). It has been suggested that PVEP is generated by activity in the X-type ganglion cells while FVEP is generated by activity in the Y-type ganglion cells (63). However, despite these suspected different origins, responses recorded in the LGN to flash and pattern stimuli showed no significant differences in their amplitudes and latencies. These differences became apparent only in the higher visual centers of the brain (64).

Origin of the Signal

The gross VEP

When recording VEP's the signal may be "contaminated" with artifacts such as muscular and cardiac activity, and respiration. In the dog it has been reported that the VEP signal may also be contaminated with far-field ERG activity (65). However, most of these artifacts can be eliminated by careful selection of sites for the reference and ground electrodes, and by restricting the recording to signals time-locked with the stimulus.

Another possible source of signal contamination is from the pathways leading from the retina to the visual cortex. While most of the retinal axons relay their information to the striate (and in some species to the extrastriate) cortex via the LGN, some axons take a less direct route. These fibers run

from the retina to the superior colliculus, and from there, via the pulvinar or the lateral posterior nucleus of the thalamus, to extrastriate visual areas (26). This pathway is primarily involved in location of objects in the visual field, shifting of visual attention and control of eye movements (66). Electrical activity in this secondary pathway may also interfere with the recording of the VEP (67). Again, this interference may be partially eliminated by judicious placement of the electrodes over the occipital lobe.

When the VEP is recorded with surface electrodes placed over the occipital lobe, a significant part of the recorded signal is a result of activity of the central retina. There are two reasons for this phenomenon. The first is the magnification factor discussed earlier. Because a disproportionate area of the cortex is devoted to processing information from the fovea or area centralis, this region contributes a significant part of the signal (58). The second reason is the anatomy of area 17. As stated earlier, the area centralis representation is located at the crown of the lateral gyrus in the cat (20), or the junction of the dorsal and tentorial surfaces of the calcarine sulcus in nonhuman primates (68), i.e., on the exposed dorsal surface of the occipital lobe. Representations of the more peripheral visual fields, on the other hand, lie deep within the calcarine sulcus in nonhuman primates (68) or the splenial sulcus in cats (20). Therefore, the recording electrodes are physically

located directly over the representation of the area centralis, while representations of the peripheral fields are far less accessible.

The neuronal basis of VEP's

Visual evoked potentials represent the sum of the electrical activity of cortical neurons following visual stimulation. This activity may be the result of synaptic depolarization causing excitation (EPSP) or hyperpolarization causing inhibition (IPSP). Furthermore, in the same cell, a primary EPSP event may be followed by an IPSP, or vice versa (69). Therefore, some intracellular recordings yield results very similar to surface VEP recordings, while in other cases the two recordings produce different signals.

While the generator sites for other evoked potentials, such as auditory brainstem evoked potentials, have been precisely located, this has not been the case for VEP's. Nevertheless, a few general statements can still be made. Inhibitory post synaptic potentials dominate during the positive phases of surface recorded VEP's, while EPSP's prevail during the negative surface waves (70). Both EPSP and IPSP are tuned to the preferred direction or orientation of the stimulus (71). In cats the first positive deflection of the VEP wave reflects the activity of afferent geniculocortical on-center fibers and of about 1/3 of the cortical neurons in layer IV (69). The following large positive deflection is a result of a GABA-mediated primary IPSP in a

large population of cortical neurons (69). The negative components of the VEP wave reflects a late, less synchronized EPSP of a large proportion of cortical cells (69).

In electrophysiological studies of man and nonhuman primates, it is customary to identify the VEP peaks based on their latency rather than the order of their appearance (72), though the waveforms are sometimes similar to those of non-primates. It has been reported that when the FVEP of nonhuman primates and cattle are compared, a homology is found between P15 and P1, N40 and N1, P65 and P2, and N95 and N2 of the monkey and cow respectively (73). Similar homologies have been proposed with the P40, N70, P100, N130 and P170 of the FVEP in man (72), and with P1, N1, P2, N2 and P3 in the canine FVEP (74). Based on these homologies, it has been suggested that in both dogs and cattle P1 originates at a subcortical source, primarily the thalamocortical radiations (73, 74). N1 represents excitatory postsynaptic potential from thalamocortical fibers onto neurons in lamina IVA and IVCb of the striate cortex (73, 74). P2 represents inhibitory postsynaptic potentials from stellate cells onto other neurons in lamina IVCb of the striate cortex (73, 74). N2 represents stellate cell input to layer III of the striate cortex (73, 74). P3 is the result of poststriate activity (73, 74). However, as mentioned earlier, the question of the location of the generator sites has not been unequivocally resolved. Some researchers have suggested that the P2 peak of the feline FVEP

is a retinotectal pathway signal transmitted to the extrastriate cortex (62). Other studies concluded that the origin of P1 in rats is cortical rather than subcortical (56).

Stimulus Parameters and Their Effect on the PVEP

Visual Refraction

A great effort was made in these experiments to ensure the high optical quality of the stimulus image. The equipment design made it possible to visualize the image on the canine fundus and to focus it in order to achieve maximum image quality. This quality control was necessary because the PVEP is more sensitive to small refractive errors than the ERG (75). A one-diopter (D) error can reduce the PVEP amplitude by 30%, and a four-D error can cause the wave to approach zero amplitude (75). Refraction also affects the latency of the PVEP, and this effect is proportional to the spatial frequency of the stimulus (76).

Retinal location and field size

Due to the limited objective of these experiments, the stimulating pattern was centered on the canine area centralis. However, the location of the stimulus in the retinal field can have a considerable effect on the signal recorded, though this effect is, once again, spatial frequency dependent (58). Maximal PVEP amplitudes are recorded when narrow gratings (<20 minutes of arc) are used to stimulate the central 2-3 degrees of the retina in man (77, 78). Using these same patterns to stimulate parafoveal regions results in a significant

reduction of PVEP amplitudes (77, 78). The parafoveal and peripheral areas of the retina generate larger PVEP signals as the spatial frequency of the stimulus is decreased, especially outside the 6-12 degree isopter (78, 79). These phenomena are probably a result of the distribution of cones and rods in the retina, and the fact that lower spatial frequency stimuli tend to produce more of a luminance, rather than pattern, response (58).

Photoreceptor concentration also explains the finding that in the more peripheral retina, larger stimulating fields are needed to evoke the same response that smaller fields evoke in the central retina (77). In the central retina PVEP amplitudes increase linearly with the diameter of the stimulated area, though the use of an annular stimulus can cause a reduced response, probably due to center-surround antagonism (80).

Spatial frequency

It is well established that PVEP amplitudes are related to the spatial frequency of the stimulus (81-87). Many researchers describe the spatial frequency-PVEP amplitude function as a tuning function (85, 86). This function displays a maximum PVEP amplitude with stimuli 10-20 minutes of arc in size, with a drop in amplitude when the grating size is increased or decreased (81, 82). More careful analysis of the data suggests that this tuning function may be bimodal (i.e., containing 2 peaks) (85, 86). This result, and the varying

reports on the most "effective" spatial frequency, may be due to variations in electrode positioning, since different cortical regions, and even individual neurons, may possess different spatial tuning characteristics (88).

However, when wide gratings (>30 minutes of arc) are used as stimuli the PVEP signal becomes more luminance-, rather than pattern-, dependent (58), and some researchers suggest that at these frequencies the PVEP amplitude levels off rather than decrease (83). These conflicting results are probably due to the fact that the effect of spatial frequency on PVEP is also dependent on the temporal frequency and contrast of the stimulus (84, 88).

In man it has been shown that the P200 peak is most sensitive to changes in spatial frequency, while the P100 is hardly affected by these changes (87). In rats, on the other hand, both the latency and amplitude of P1 are reportedly affected by the spatial frequency of the stimulus (84).

Stimulus contrast

Changing the contrast of the stimulus has different effects on the amplitude and latency of the PVEP. At low contrast levels, the relationship between contrast and PVEP amplitudes is linear (89, 90), with a shallow slope (88). At higher contrasts, the function has been described either as nonmonotonic (89), or a linear relation of the amplitude to log contrast (90, 91), with a steep slope (88). On the other hand, the latency of the signal decreases as the stimulus

contrast (84, 92) or log contrast (91) is increased. In rats, the contrast function of the amplitude of the second harmonic of PVEP also consists of two linear segments: one for low contrasts with a shallow slope and one for high contrasts with a steep slope (84). The fact that these two distinct components have been found in both rats and primates suggests the existence of 2 separate contrast mechanisms (84).

Stimulus luminance

The effect of luminance on the PVEP is closely related to the spatial and temporal frequencies of the stimulus. It is generally agreed that luminance is best perceived at intermediate spatial frequencies, suggesting the existence of a bandpass filtering mechanism (93, 94). PVEP recordings in rhesus monkeys have shown that the perception of gratings composed of luminance contrast peaks at four cycles per degree (cpd), and drops at lower and higher spatial frequencies (94). Similar results were obtained in cats and rats, but it is also reported that in these species the signal latency increases as a function of spatial frequency (84, 95).

The effect of the temporal frequency of the stimulus on luminance perception is more controversial. Some researchers claim that similar bandpass filtering of PVEP signals takes place when the temporal frequency of the stimulus is changed, and that contrast perception peaks at a frequency of 5-15 Hz (93). Others suggest a lowpass tuning phenomenon in the

temporal domain, with contrast perception dropping at frequencies >3 Hz (94).

Background luminance can also affect the PVEP recording. In high background luminance peak N100 is dominant, while N150 is barely noticeable (96). As the background luminance is decreased, the situation is reversed, and N150 becomes the dominant negative peak (96).

Temporal frequency

As stated previously, the effect of the temporal frequency of the stimulus on PVEP is also dependent on the spatial frequency and contrast. When plotting PVEP amplitudes vs. temporal frequency in nonhuman primates, a sharp tuning curve is obtained, with the largest signal recorded at a frequency of approximately 15 Hz (88). However, even at this "optimal" frequency, the signal will depend on the spatial frequency (88). On the other hand, the signal's phase lag, or latency, increases with increasing temporal frequency, and this increase is more pronounced at higher spatial frequencies (88). It has also been reported that at very low temporal frequencies (<2 Hz.) the PVEP becomes more transient, rather than steady-state, in its nature (92). Thus, the PVEP shifts from a transient, bandpass type of temporal response at low spatial frequencies, to a sustained, low-pass response at high spatial frequencies (97). This characteristic has indeed been found to be similar to the properties of the receptive field of a single X-type feline ganglion cell (98).

Stimulus wavelength

Electrophysiological recordings can be used to measure spectral sensitivity in humans viewing alternating bars of equal brightness but different wavelengths. Pattern VEP recordings are much more sensitive than ERG recordings at detecting subtle wavelength differences (99). Both the PVEP amplitude and latency measurements provide a spectral sensitivity curve which is in good agreement with the standard CIE photopic function and with psychophysical studies, with retinal sensitivity peaking at 570 nm (99).

The effect of chromatic changes in the stimulus on the PVEP is, once again, dependent on the temporal and spatial properties of the grating pattern. Chromatic sensitivity is highest at low spatial and temporal frequencies, suggesting the existence of a lowpass filtering mechanism (94). The greatest chromatic sensitivity in man was recorded at a temporal frequency of 0.2 Hz (97). At lower frequencies, chromatic perception drops, and disappears at 0.01 Hz (97).

Electrode placement

It is hoped that the results of this work will assist in the development of a protocol for PVEP recordings in the dog, similar to that which exists in the cat (60). As previously noted, one of the most important considerations in carrying out successful PVEP recordings is the precise location of the recording and reference electrodes. Displacement of the active cortical electrode by as little as 5 mm can cause a decrease

of up to 25% (depending on the spatial frequency of the stimulus) in the amplitude of the PVEP in the dogs (Dawson, personal observations). In humans, the respective figures are 2.5 cm and 75% (100). In the cat, the latency of cortical responses to flash stimuli was not significantly affected when different active electrode positions were used, but the amplitude of the signals changed by as much as 280% (60). Positioning of the reference electrode may affect the contamination of the PVEP signal by far-field potentials such as ERG (55, 65, 96).

Visual evoked potentials and psychophysical testing

Visual evoked potential recordings are frequently highly correlated to psychophysical test results, and it is this fact that makes the VEP such as an effective research and diagnostic tool (58). In humans, PVEP refraction agrees quite well with Snellen chart refraction (58). The PVEP refraction technique has been refined so that both sphere and cylinder corrections can be quickly determined (101). The spatial tuning curve of the PVEP in rhesus monkeys parallels the psychophysical sensitivity falloff reported in these nonhuman primates. Electrophysiologically- and behaviorally-determined visual resolutions in the dog also produce similar results (102).

The psychophysical contrast threshold in man is in close agreement with the threshold of P100 (88-90), which is the most contrast sensitive component of the human PVEP (92). The

spectral sensitivity of man as determined by VEP's and psychophysical testing is also very similar (58). This similarity has been documented both with FVEP's (103) and PVEP's (99). Peak VEP sensitivity occurs at 570 nm under photopic conditions (99) and at 500 nm under scotopic conditions (58).

Visual evoked potentials are also very sensitive to cerebral lesions in both rats (79) and humans (104). In rats, even small, focal lesions have a significant effect on the VEP, though the effect varies for FVEP's and PVEP's (79). This difference in the effect on the two types of VEP's once again hints at the existence of different generation sites for these two potentials (79). In man FVEP's and PVEP's are also differentially affected by cerebral lesions (104). Latency of the signal is the parameter most altered in FVEP's, while amplitude of the signal is the parameter most affected in PVEP's (104). Pattern VEP's recorded using a multichannel system accurately pinpoint the location of cerebral lesions in man (104).

VEP's and Glaucoma

Visual evoked potentials are regarded as an especially useful tool in the early diagnosis of glaucoma, since frequently they display abnormalities long before other clinical changes, such as optic disc cupping, become visible (105-107). Patients suffering from ocular hypertension also

have a high percentage of abnormal PVEP recordings, even though their visual fields are still normal (108-110).

When a flash stimulus is used to elicit FVEP in glaucomatous patients, signal latency (111) and P2 amplitude (112) are unchanged. However, the amplitude of P1 is reported to decrease significantly, and the extent of this decrease is correlated with the stage of the disease (112). When the flash frequency is altered, it is revealed that the loss is evident mostly at high (>13 Hz) flicker rates (110, 113). It has been suggested that this is because at the early stages of glaucoma there is a preferential loss of Y-type retinal ganglion cells which are indeed more responsive to high frequency stimulation (113). However, other researchers report that these changes in the signal can be reversed if the IOP is lowered, thereby suggesting the existence of a different mechanism (111).

Most PVEP parameters, including amplitude, latency, contrast threshold and/or slope, are also abnormal when a pattern is used as stimulus (107). These changes are, once again, dependent on the spatial and temporal frequencies of the stimulus used. The changes in the latency of the PVEP signal in glaucomatous patients is most pronounced at low spatial- and high temporal-frequencies (109). The latency of the average signal increases by 8 msec, with more pronounced changes as the disease progresses (109). Loss of contrast sensitivity (106) and PVEP amplitudes (105) are also most

evident at low spatial and high (8 Hz) temporal frequencies. A 50% drop in PVEP amplitudes can be recorded as early as 2 weeks after glaucoma is experimentally induced in nonhuman primates (105). By 16 weeks, signals drop to nearly 1/3 their normal amplitude (105). In people suffering from advanced glaucoma, the PVEP waveform can become so distorted that identification of the various peaks and analysis of the signal is all but impossible (108).

As is the case with the flash VEP, the existence of two segregated pathways is the probable cause for the spatial and temporal tuning properties of the PVEP in glaucoma (106). In both nonhuman primates and cats, Y- (or alpha-) type retinal ganglion cells are sensitive to stimuli possessing a low spatial and a high temporal frequency (114, 115). These neurons, which project to the magnocellular layers of the LGN, possess large diameter axons which have been shown to be preferentially damaged in induced glaucoma in nonhuman primates (116). It is worth noting that while magnocellular and parvocellular systems have yet to be documented in the dog, the preferential loss of large diameter axons has been demonstrated in the optic nerve of chronically glaucomatous Beagles (117).

CHAPTER 2
MATERIALS AND METHODS

Experimental Animals

A total of 12 dogs were used in the study. The age, sex, breed, eye disease status and stimulated eye of all dogs used in this study are summarized in Table 1.

TABLE 1
EXPERIMENTAL ANIMALS

Dog designation	Age (in years)	Sex ^a	Breed ^b	Status ^c	Stimulated eye
Oa	7.6	F	B	N	left
Kd	10.0	F	B	N	right
Jl	5.3	M	B	N	right
Sd	6.0	M	B	N	left
Oe	10.6	F	B	N	right
Bo	7.8	M	B	N	right
Be	4.9	M	B	N	left
Pa	3.1	F	B	G	left
Se	1.8	M	B	G	right
Kf	3.3	F	H	N	left
Br	4.0	M	H	N	left
Bn	4.7	F	H	N	right

^aSex: F--female M--male

^bBreed: B--Beagle H--Greyhound

^cStatus: N--normal G--Glaucomatous

Nine of the 12 dogs were Beagles. Beagles were chosen since it is the canine breed most frequently used in research and stereotaxic mapping of the Beagle's brain is published (118). Two of the Beagles were pre-glaucomatous dogs from a

colony with hereditary primary open angle glaucoma (POAG) (119). These dogs were used to study the possible effect of glaucoma on the location of the cortical area of central vision in the dog, or, if as expected, no effect was found, to increase the size of the sample. Mapping was also conducted in three Greyhounds, for inter-breed comparison purposes. Greyhounds were chosen due to their distinctly different head size and shape. Recordings were conducted only on normal or pre-glaucomatous dogs.

It has been reported that VEP measurements in dogs stabilize by age 100 days (53); all dogs used in this study were much older. Every dog used in the study underwent a clinical and ophthalmological examination on the day of the experiment.

Surgical Protocol

Use of dogs in this study was approved by the Institutional Animal Care and Use Committee of the University of Florida as project #0106.

Dogs used in this study were deprived of food the previous evening, but had unrestricted access to water. Animals were premedicated with 0.01 mg/kg of glycopyrrolate I.M., to reduce secretions and stabilize cardiac function. The animal was then catheterized and injected with 15 mg/kg thiamylal, I.V. The dog was intubated and placed on halothane anesthesia, using a mixture of 25% oxygen and 75% nitrous

oxide. The initial halothane concentration was 3%, and was reduced to 1% after the animal reached a surgical plane of anesthesia.

The animal was placed on a hot water blanket, and a rectal thermometer was used to monitor body temperature. An EKG was used to monitor cardiac function, and the eyelids were sutured to prevent the cornea from drying during the operation. The dog's head was then mounted in a stereotaxic device, and local injections of lidocaine were used to relieve any pain that might result from use of the ear-bars.

A lateral rostrotentorial craniotomy operation was performed to expose the presumed location of V I in the occipital lobe (120). A horseshoe-shaped skin incision was made, extending from the ear to the dorsal midline, and curving cranially to the lateral canthus of the eye. The underlying muscles were severed along the nuchal crest, and reflected ventrolaterally. Compression, ligation and coagulation were used to minimize bleeding. The muscles were scraped off the skull using a periosteal elevator. An electric drill was then used to create the initial hole in the bone. This hole was then expanded with a Lampert rongeur until an opening with the following borders was obtained: 0.5 cm rostral to the nuchal crest and lateral to the dorsal midline; rostrally, at the orbit and frontal sinus; and ventrally at the temporal musculature, zygomatic arch and coronoid process of the mandible (120). Bleeding from exposed sinuses was

controlled with vitamin K injections (2 mg/kg, I.M.) given 24 hours pre-op (121), and with gelfoam and bonewax inserted into the sinuses during surgery. The dura was reflected using the tent-flap method and cut with iris scissors. The edges of the wound were treated with local injections of lidocaine, but no drug came in contact with the exposed cortical surface.

Following the operation, the dog was taken off the anesthesia, and its muscles relaxed with an injection of pancuronium (0.1 mg/kg, I.V.). A respirator, delivering the same oxygen-nitrous oxide mixture, was used to ventilate the dog. End-tidal CO₂ levels were monitored and maintained at a range of 4.4-4.7%. Additional injections of pancuronium were administered when needed, approximately one injection every 45 minutes.

Great care was taken to ensure that the cortical tissue remained viable following its exposure. After reflecting the dura, a plastic chamber was mounted over the exposed brain and filled with warm mineral oil to prevent the pia from drying (17). To prevent brain edema once the dura has been reflected, dilute mannitol (0.625%) was added to the fluids which the dog was receiving. This was supplemented by I.V. injections of dexamethasone and mannitol as needed. No dog received more than 50 ml of mannitol (25%) and/or 6 mg of dexamethasone (121).

Electrophysiological Mapping of the Area of Central Vision

Electrode Placement

The contralateral pupil was dilated using tropicamide and covered with a contact lens in which a platinum wire has been embedded. This lens served as an active electrode for the simultaneous recording of PERG signals; its reference electrode was placed at the medial canthus (122). A 2 mm diameter silver ball tipped wire (32, 123) mounted on the stereotaxic device served as the active electrode for the unipolar recording (8, 13) of PVEP's. As the area centralis was being stimulated, this active cortical electrode was moved, using the control dials of the stereotaxic device, in a search grid-like manner on the exposed surface of the cortex. The increments of movement were 2 mm. This distance was used by Woolsey and Talbot in their mapping studies (8), and was shown by Hubel and Wiesel to correspond to the size of one aggregate receptive field in the cortex (32). The cortical reference electrode was attached to a screw mounted on the skull just rostrally to the bone lesion. The dog was grounded through the earbars of the stereotaxic device.

The Stimulus

Using a modified Bausch & Lomb table mounted ophthalmoscope, a computer generated counterphased image was

projected on the fundus of the eye. Visual control was used to carefully position and focus the image on the area centralis of the retina (Figure 4). The image consisted of square wave contrast, vertical, dark and light bars. The stimulated retinal field was 15° in diameter, based on a mean retinal axial length of 18 mm (124) and a mean optic disc diameter of 1.8 mm (125). The stimulated field was surrounded by a luminated field $45^{\circ} \times 75^{\circ}$ in size.

The width of an individual bar was 16 minutes of arc/phase. Bars were alternated in a square-wave fashion 0.5 cycles (1 bar width) at 2.5 Hz. The stimulus had a mean luminance of 1.4 log Fl, with 70% contrast of the bars. The luminance of the surround field was 0.3 log units higher than the luminance of the light bar of the dark/light bar pair, to suppress the effect of any scattered light. The room was darkened.

Signal Processing

The analogue/digital converter used to record the VEP's was time-locked to the phase shifting of the stimulus, so that any signals not synchronized with the stimulating pattern were reduced. As described previously, the active cortical electrode was moved at increments of 2 mm on the surface of the cortex while the area centralis was being stimulated. At each new recording site, a sample of 100 signals was collected. Signals picked up by the electrode were amplified

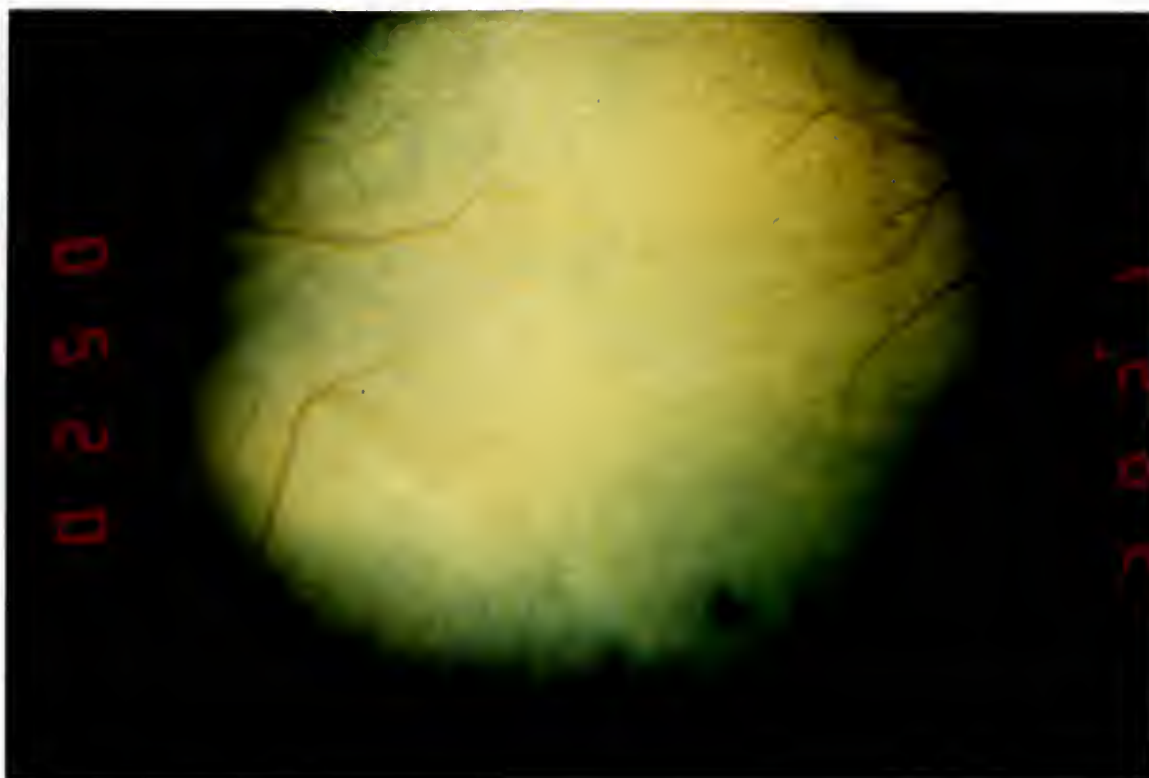


Figure 4. The canine area centralis.
Picture is of a typical, normal, Beagle. For
detailed description of the area, see the text.

X10,000 with a 2-300 Hz (3dB) bandpass and digitized. The 100 signals were then summed to reduce random noise, and the result was displayed on a screen and stored on a magnetic disk for future analysis.

Electrical signals produced by counterphasing of light and dark grating bars were indicators of the functional nature of the area centralis pathways as the retina and visual cortex responded to stimulation. The signals' root mean square (RMS) amplitude at each recording site was calculated off-line and provided an unbiased estimate of the magnitude of the responses (126). The simultaneous recording of PERG signals was intended to rule out any variables which may affect the VEP signals. As long as the ERG signals were consistent, any variation in the VEP signals could have resulted only from the movement of the active electrode on the surface of the cortex.

Histological Studies of the Area of Central Vision

Marking the Location of the Area of Central Vision

Following the electrophysiological recordings, the dog was euthanized with an overdose of intravenous pentobarbital sodium. Photographs were taken of the site which yielded the signal with the highest amplitude. A Hamilton microliter syringe (33 ga., 1/2 in.) was then mounted on the same stereotaxic device, and used to inject 2.0 μ L of fluoro-gold at the same site (127). Fluoro-gold is a fluorescent retrograde axonally transported tracer that provides intensive

labelling which does not fade over long periods of time (128). This tracer was chosen as a marker because it is an extremely stable compound and therefore compatible with numerous other histochemical procedures (129).

Since numerical values for signal RMS amplitude and latency were not available at this stage of the experiment, it was decided to inject the tracer at the site generating the signal with the highest amplitude. The site was chosen by looking at the signals on the oscilloscope, and it was felt that the signal with the highest amplitude could be identified more reliably than the signal with the shortest latency. This decision was later validated by the statistical analysis of the electrophysiological results (see Chapter 3). The tracer was injected 1 mm below the surface of the cortex. A nine cm² block of cortex surrounding the injection site was then removed from the brain.

Processing and Staining

The block of cortical tissue which was removed from the brain was trimmed, and the white matter was notched for orientation purposes. After peeling off the pia mater, the specimen was fixed by immersion fixation (13, 17, 36) in a 4% paraformaldehyde solution containing 5% sucrose (by weight). Shrinkage resulting from this fixation method (13, 17, 36) has been estimated at 25%, and accounted for.

Following fixation, the block was frozen (in dry ice), and sectioned coronally at 40μ using a sliding freezing microtome. Each specimen was serially sectioned approximately 290 times. The sections were arranged in 6 parallel series in trays containing diluted (1:10) fixative and mounted on gelatin (0.5%) subbed slides (3 sections per slide). Sections in alternate series were processed for the fluoro-gold tracer or stained for either the cyto-architecture or the myelo-architecture of the cortical tissue.

The stains used in this study were chosen based on mapping studies in other species (16, 35). Standard cresyl-violet (c. v.) stain was used for the cyto-architectural series (16), and standard Weil stain was used for the myelo-architectural series (35). The slides were then viewed through a light microscope to find those sections containing the cyto- and myelo-architectural characteristics of the area of central vision as presented in Figure 1 (see Introduction).

Slides in series undergoing fluoro-gold processing were dehydrated and defatted (127). The slides were then mounted with fluoromount and cover slipped. Fluoro-gold labelling of the sections was viewed by fluorescence microscopy (UV light). Since the tracer was injected at the site which yielded the highest amplitude signal, sections containing the fluoro-gold stain were interpreted to represent the electrophysiologically determined area of central vision. The distance between the

electrophysiologically- and histologically-determined areas of central vision was then calculated, based on a distance of 40μ per section.

Photography

Sections containing the histological characteristics of the area of central vision or the fluoro-gold tracer were photographed. Neutral density filters were used, when needed, to keep the exposure time under 0.5 seconds. Magnification was X12.5. Sections stained with c. v. or Weil stains were photographed both in black and white and color film. Black & white prints were obtained using Kodak Technical Pan film (100 ASA). For comparison purposes, pictures were taken both with and without a yellow filter. Color slides were obtained using Kodak Ektachrome 50 film. A Kodak Ektachrome P800 (400 ASA) film was used to photograph the sections containing the fluoro-gold tracer.

Potential Problems in the Experimental Design

Use of Halothane as a General Anesthetic Agent

It is important to remember that in this study, halothane was used during surgery, but not during the recording session itself. During the craniotomy, the dogs were anesthetized using a low (<1.5%) concentration of halothane. However, after the cortex was exposed the use of halothane was discontinued. At least 90 minutes (needed to set up the electrodes and solve

electrical noise problems) would then pass before the beginning of the recordings. While this may not be sufficient time for all of the halothane to be eliminated from the cortex, other studies have shown that near normal electrophysiological recordings can be conducted after this time period (39, 43, 65, 130-134).

It is known that inhalation anesthetics affect, sometimes profoundly, cortical activity. However, this does not suggest that all brain or retinal activity ceases during anesthesia. The brainstem, for example, is hardly affected by halothane (132). The agent is recommended for use as an anesthetic in recording brainstem auditory evoked potentials (BAEP's) (132). In the retina (an extension of the central nervous system) halothane has been found to have no effect on the decay time course of rod and cone late receptor potential (133). In the canine retina, DC--recorded a-- and b--waves are only mildly changed in the presence of 2% halothane (131). Even the c-wave, which is usually significantly reduced by halothane in the dog, has on occasion been potentiated in the presence of halothane (131), as has the b-wave of the rabbit ERG (135).

The effect of halothane on the electrophysiology of the visual cortex is controversial. While some researchers claim the agent has profound effects on VEP recordings, others report the effect to be minor (39, 43, 65, 130, 134, 136). Halothane/nitrous oxide anesthesia is reported to have a very moderate effect on qualitative properties, such as the

preferred orientation and direction of stimuli movement, of neurons in the visual cortex of cats (134). Indeed, Tusa et al. used an anesthetic protocol very similar to the one used in this study when mapping the retinotopic organization of areas 18-21 of the cat's visual cortex (39, 43). In their experiments, halothane was used for the surgical preparation of the animal, and then the animal was paralyzed for the recording session. Other researchers who recorded VEP's in dogs went a step further and performed their recordings while the animal was still under halothane anesthesia (65, 130). Since the clearance time of halothane from the canine central nervous system is less than 40 minutes (136), and dogs used in these experiments were taken off halothane 90 minutes prior to the recordings, it is reasonable to assume that halothane did not interfere significantly with the cortical signals recorded from these dogs.

Determining the Location of the Canine Area Centralis

The anatomically-determined area centralis of the dog is a horizontally-oriented oval region (Figure 4) (137). It is located in the tapetal fundus, approximately one disc diameter dorsal, and 2 disc diameters temporal, to the optic disc (138, 139). Fundoscopically, the area appears to be free of visible blood vessels, but it does contain a capillary network (115). As expected, this area contains the greatest concentration of cones (5.1 per 50 μ field) in the canine retina (140), and the

greatest concentration ($>5,000/\text{mm}^2$) of ganglion cells (137). Therefore, the decision on where to project the stimulus field was made based on the relation to the optic disc and the absence of visible blood vessels.

Pain to the Animal and its Possible Influence on the Signal

All possible precautions were taken to minimize pain to the animals used in this study. The animal was anesthetized using halothane and a mixture of 75% nitrous oxide and 25% oxygen. Mounting of the animal in the stereotaxic device and all surgical procedures were performed under surgical anesthesia. After the craniotomy, and prior to the removal of the animal from the halothane, the regions in contact with the ear-bars and the edges of the wound were injected with 2% lidocaine hydrochloride. No tissue manipulations were undertaken once the halothane administration had stopped. During the entire recording session, the animal was ventilated with the same nitrous oxide-oxygen mixture.

Once the animal was removed from halothane, it may have experienced some discomfort due to its inability to change its position, the use of the stereotaxic device and the surgical wound. However, it is believed that the use of nitrous oxide and lidocaine kept this discomfort at a minimal level. Close attention was paid, throughout the experiment, to any signs of pain. Core temperature, heart rate, end-tidal CO_2 levels and, obviously, cortical signals, were constantly monitored as

indicators of pain. In none of the recording sessions did we note any significant changes in any of these indicators.

CHAPTER 3 RESULTS

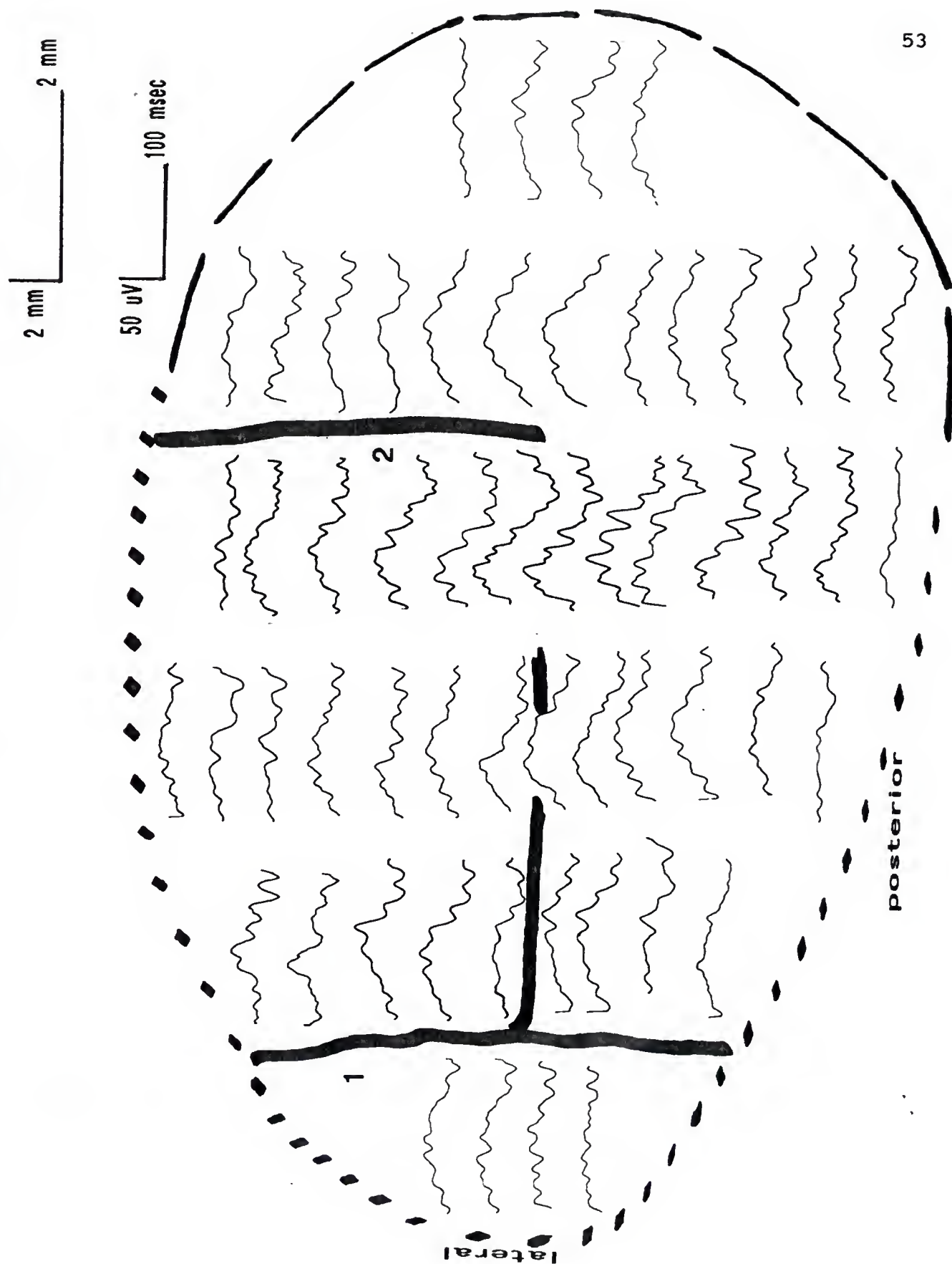
Results in a Typical Dog

The distribution of signals recorded from one representative normal Beagle (Bo) is shown in Figure 5, along with landmarks of the cortical surface. As explained earlier, the distance between two adjacent signals was 2 mm. It can be seen that signals with the highest RMS amplitude (up to 59 μ V) and shortest latency (as low as 29 msec) are clustered around the junction of the marginal and endomarginal sulci. The decrease in signal amplitude and increase in signal latency as the electrode was moved from this region can be appreciated. The stereotaxic coordinates of the sites generating the signal with the highest RMS amplitude and the signal with the shortest latency in this dog are presented in Table 2 and Figure 6. The fluoro-gold tracer was injected at the site generating the signal with the highest amplitude, and served as a marker for the histological analysis (Figure 7).

Results in Normal Beagles

The location of the cortical area of central vision in normal Beagles was determined by analysis of the electro-

Figure 5. Distribution of signals on the cortical surface. Signals recorded from dog Bo are presented. Long dashes--border of surgical exposure. Short dashes--border of responsive area. Cortical landmarks: (1) Marginal sulcus. (2) Endomarginal sulcus. Top scale bars--distances over cortical surface. Bottom scale bars--signal parameters.



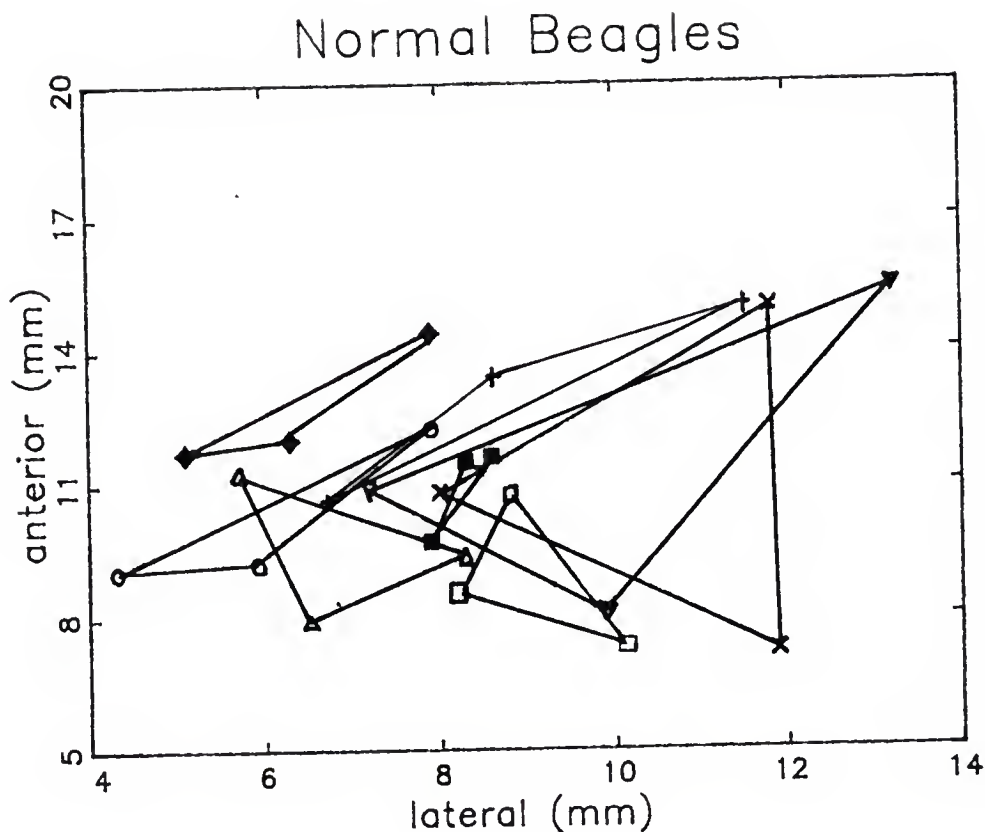


Figure 6. Location of the cortical area of central vision in normal Beagles.

The location of the cortical area of central vision in seven normal Beagles was determined by the RMS and latency of the electrophysiological signal and by the cytoarchitecture and myeloarchitecture of the histological slides. The three sets of coordinates determined in each dog have been connected by lines to form a triangle.

X axis--Distance (in mm) lateral to the midline.

Y axis--Distance (in mm) anterior to the IAP.

(□)--Dog Oa (○)--Dog Kd (Δ)--Dog J1

(+)--Dog Sd (X)--Dog Oe (◆)--Dog Bo

(▽)--Dog Be (■)--Mean coordinates in normal Beagles

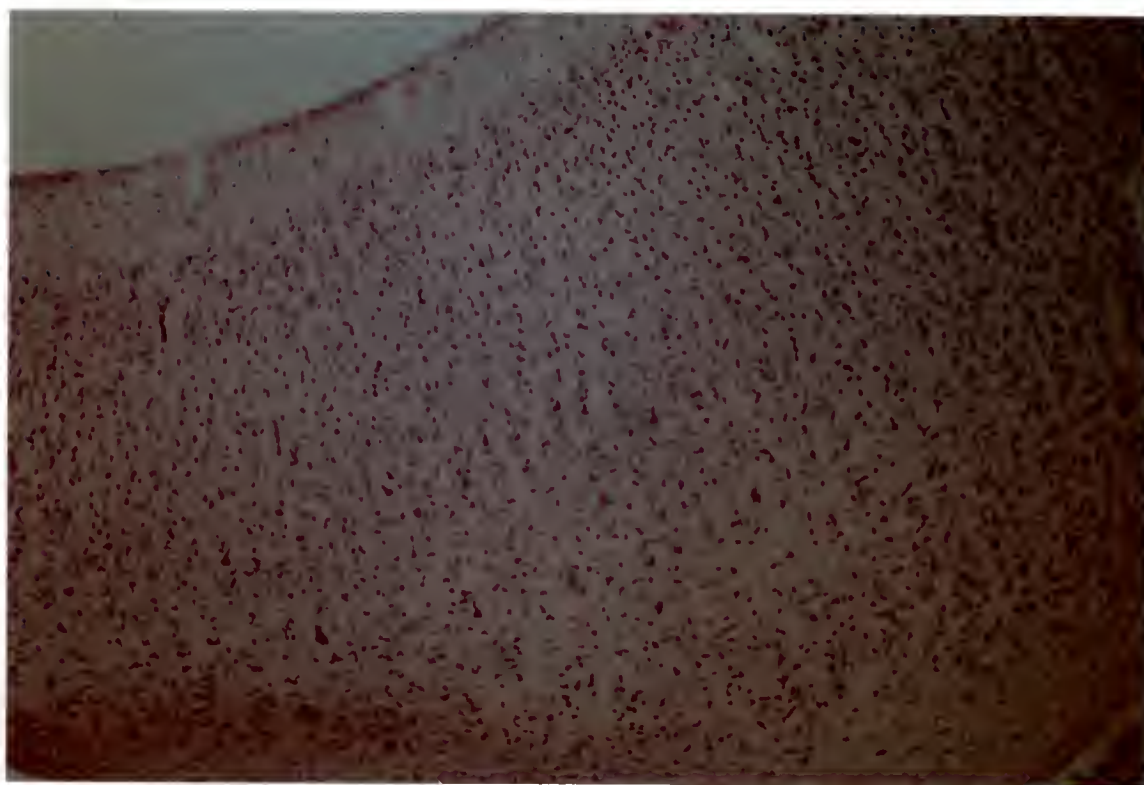


Figure 7. Histological location of the cortical area of central vision. Magnification x 12.5.

a) A 40μ coronal section stained using c.v. stain to illustrate the cytoarchitecture of the region. The striate cortex, at the right, is a granular region with large pyramidal cells in layers III and V, and with small, densely-packed cells in layer IV. The parastriate cortex at the left is also granular, with layer III containing a greater number of large pyramidal cells, but layers IV and V have far fewer cells than in the striate cortex. The needle tract resulting from the injection of fluoro-gold can be seen at the left corner.

b) A 40μ coronal section stained using Weil stain to illustrate the myeloarchitecture of the region. In the striate cortex on the left the heavily myelinated outer stripe of Baillarger is visible in layer IV, and the inner stripe of Baillarger is seen in layer VI. The parastriate on the right is far less myelinated. The needle tract resulting from the injection of fluoro-gold can be seen at the right corner.



Figure 7--continued

physiological signal recorded, and by the cytoarchitecture and myeloarchitecture of the histological sections of the brain. Sites with the highest RMS amplitude signal, the shortest latency signal and the typical histological characteristics were designated as the cortical area of central vision as determined by each technique. The results in seven normal Beagles are presented in Figure 6. The coordinates of the cortical area of central vision in these seven dogs, as determined by each technique, together with the mean results for this experimental group, are presented in Table 2.

Two methods of statistical analysis were used to evaluate the three mapping techniques. Results obtained by each mapping technique were compared to the results obtained by the other two techniques using multiple Student's t-tests. There were no significant differences between the results obtained by any of the three mapping techniques at neither the anterior-posterior axis ($p > 0.18$) nor at the medial-lateral axis ($p > 0.64$). An analysis of variance (ANOVA) test yielded similar results. There were no significant differences between the three mean coordinates, at neither the anterior-posterior axis ($p = 0.32$) nor at the medial-lateral axis ($p = 0.85$). Parametric methods of analysis were used based on the assumptions that the population of Beagles is normally distributed and that the sample was randomly chosen.

A second method of analysis was to calculate the distances between the three sets of coordinates obtained in

TABLE 2
RESULTS IN NORMAL BEAGLES

Dog	Mapping technique ^a	Coordinates ^b		Distance between coordinates (in mm) ^c
		AP axis	ML axis	
Oa	A	10.7	8.8	AL=3.6
	L	7.3	10.1	HL=2.2
	H	8.5	8.2	HA=2.3
Kd	A	9.2	5.9	AL=1.6
	L	9.0	4.3	HL=4.8
	H	12.2	7.9	HA=3.6
Jl	A	7.9	6.5	AL=3.4
	L	11.2	5.7	HL=3.2
	H	9.3	8.3	HA=2.3
Sd	A	15.0	11.5	AL=3.3
	L	13.4	8.6	HL=3.4
	H	10.6	6.7	HA=6.5
Oe	A	15.0	11.8	AL=7.8
	L	7.2	11.9	HL=5.3
	H	10.8	8.0	HA=5.7
Bo	A	12.0	6.3	AL=1.2
	L	11.7	5.1	HL=3.9
	H	14.4	7.9	HA=2.9
Be	A	10.9	7.2	AL=3.9
	L	8.1	9.9	HL=8.0
	H	15.4	13.2	HA=7.5
Mean ^d	A	11.5 ±1.0	8.3 ±0.9	AL=3.5 ±0.8
	L	9.7 ±0.9	7.9 ±1.1	HL=4.4 ±0.7
	H	11.6 ±1.0	8.6 ±0.8	HA=4.4 ±2.1

^aMapping technique used:

A--Analysis of RMS amplitude of signal

L--Analysis of latency of signal

H--Analysis of histological data

^bCoordinates (in mm) along the anterior-posterior (AP) and medial-lateral (ML) axes. All of the coordinates given are lateral to the midline and anterior to the IAP.

^cDistance between the areas of central vision as determined by:

AL--the RMS amplitude and the latency of the signal

HL--histology and the latency of the signal

HA--histology and the RMS amplitude of the signal

^dMean coordinates ± one standard deviation.

each dog, i.e., the lengths of the three sides of the triangle described by these coordinates (Figure 6). Results of these calculations are presented in the last column of Table 2. In no case were two coordinates in a given dog more than 8 mm apart, and the mean distance between any two coordinates was 4.1 mm. Multiple Student's t-tests yielded no significant differences between the three sets of distances calculated ($p>0.44$). An ANOVA test revealed no significant differences between the three mean distances ($p=0.47$), implying that the triangle described by the three mean coordinates is statistically equilateral.

Based on the overall mean of the coordinates obtained by all three mapping techniques, it was determined that the cortical area of central vision in normal Beagles lies 10.9 ± 0.6 mm anterior to the IAP and 8.3 ± 0.2 mm lateral to the midline (results are presented as mean $\pm$ one standard deviation).

Results in Pre-glaucomatous Beagles

The location of the cortical area of central vision in pre-glaucomatous Beagles was determined by analysis of the electrophysiological signal recorded, and by the cytoarchitecture and myeloarchitecture of the histological sections of the brain. Sites with the highest RMS amplitude signal, the shortest latency signal, and the typical histological characteristics were designated as the cortical

area of central vision as determined by each technique. The results in two pre-glaucomatous Beagles are presented in Figure 8. The coordinates of the cortical area of central vision in these two dogs, as determined by each technique, together with the mean results of this experimental group, are presented in Table 3.

TABLE 3
RESULTS IN PRE-GLAUCOMATOUS BEAGLES

Dog	Mapping technique ^a	Coordinates ^b		Distance between coordinates (in mm) ^c
		AP axis	ML axis	
Pa	A	13.4	10.1	AL=7.6
	L	7.7	5.1	HL=4.9
	H	11.8	7.7	HA=2.9
Se	A	11.2	7.3	AL=1.7
	L	12.8	7.9	HL=3.0
	H	13.1	10.9	HA=4.1
Mean ^d	A	12.3 ±1.1	8.7 ±1.4	AL=4.7 ±3.0
	L	10.3 ±2.6	6.5 ±1.4	HL=4.0 ±1.0
	H	12.5 ±0.7	9.3 ±1.6	HA=3.5 ±0.6

^aMapping technique used:

A--Analysis of RMS amplitude of signal

L--Analysis of latency of signal

H--Analysis of histological data

^bCoordinates (in mm) along the anterior-posterior (AP) and medial-lateral (ML) axes. All of the coordinates given are lateral to the midline and anterior to the IAP.

^cDistance between the areas of central vision as determined by:

AL--the RMS amplitude and the latency of the signal

HL--histology and the latency of the signal

HA--histology and the RMS amplitude of the signal

^dMean coordinates ± one standard deviation.

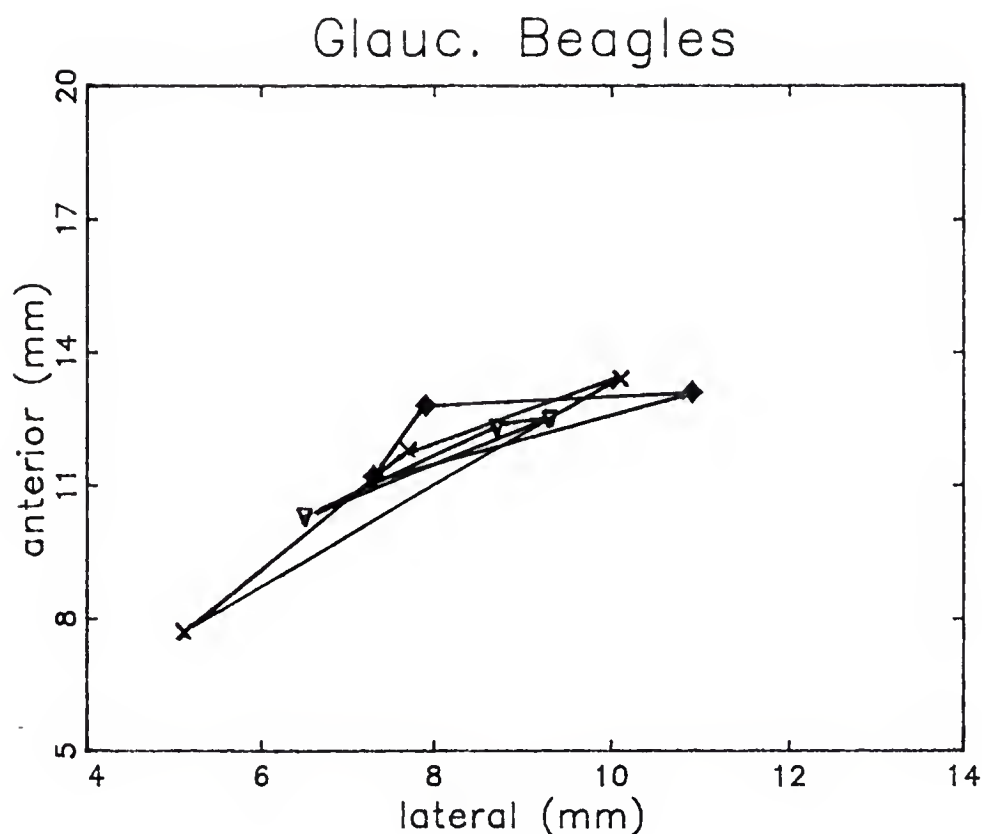


Figure 8. Location of the cortical area of central vision in pre-glaucomatous Beagles.

The location of the cortical area of central vision in two pre-glaucomatous Beagles was determined by the RMS and latency of the electrophysiological signal and by the cytoarchitecture and myeloarchitecture of the histological slides. The three sets of coordinates determined in each dog have been connected by lines to form a triangle. X axis--Distance (in mm) lateral to the midline. Y axis--Distance (in mm) anterior to the IAP.

(X)--Dog Pa (♦)--Dog Se

(▽)--Mean coordinates in pre-glaucomatous Beagles

Two methods of statistical analysis were used to evaluate the three mapping techniques. Results obtained by each mapping technique were compared to the results obtained by the other two techniques using multiple Student's t-tests. There were no significant differences between the results obtained by any of the three mapping techniques at neither the anterior-posterior axis ($p>0.49$) nor the medial-lateral axis ($p>0.32$). An ANOVA test to compare the three mean coordinates could not be conducted due to the small sample size of this experimental group.

A second method of evaluation was to calculate the distances between the three sets of coordinates obtained in each dog, i.e., the lengths of the three sides of the triangle described by these coordinates (Figure 8). Results of these calculations are presented in the last column of Table 3. In no case were two coordinates in a given dog more than 7.6 mm apart, and the mean distance between any two coordinates was 4.1 mm. Multiple Student's t-tests yielded no significant differences between the three sets of distances calculated ($p>0.73$). An ANOVA test of the three mean distances could not be performed due to the small sample size of this experimental group.

Based on the overall mean of the coordinates obtained by all three mapping techniques, it was determined that the cortical area of central vision in pre-glaucomatous Beagles

lies 11.7 ± 0.7 mm anterior to the IAP and 8.2 ± 0.9 mm lateral to the midline.

Results in Greyhounds

The location of the cortical area of central vision in Greyhounds was determined by analysis of the electrophysiological signal recorded, and by the cytoarchitecture and myeloarchitecture of the histological sections of the brain. Sites with the highest RMS amplitude signal, the shortest latency signal and the typical histological characteristics were designated as the cortical area of central vision as determined by each technique. The results in three Greyhounds are presented in Figure 9. The coordinates of the cortical area of central vision in these three dogs, as determined by each technique, together with the mean results of this experimental group, are presented in Table 4.

Two methods of statistical analysis were used to evaluate the three mapping techniques. Results obtained by each mapping technique were compared to the results obtained by the other two techniques using multiple Student's t-tests. There were no significant differences between the results obtained by any of the three mapping techniques at neither the anterior-posterior axis ($p > 0.88$) nor at the medial-lateral axis ($p > 0.30$). An ANOVA test yielded similar results. There were no significant differences between the three mean coordinates, at neither the

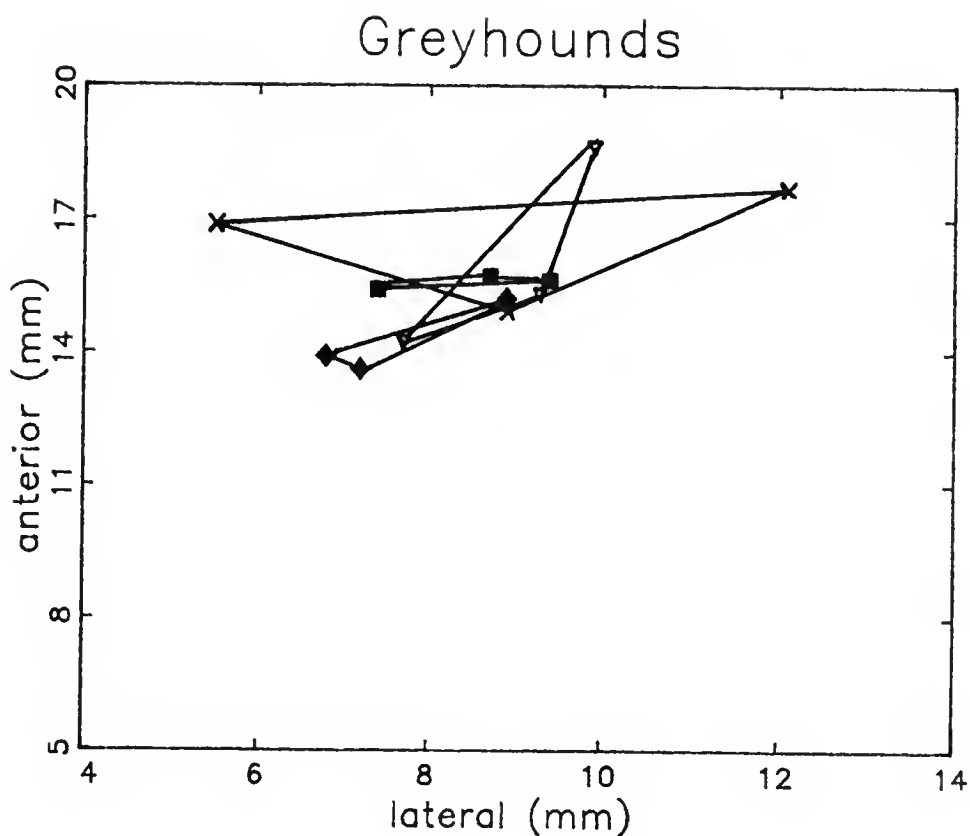


Figure 9. Location of the cortical area of central vision in Greyhounds.

The location of the cortical area of central vision in three Greyhounds was determined by the RMS and latency of the electrophysiological signal and by the cytoarchitecture and myeloarchitecture of the histological slides. The three sets of coordinates determined in each dog have been connected by lines to form a triangle.

X axis--Distance (in mm) lateral to the midline.

Y axis--Distance (in mm) anterior to the IAP.

(X)--Dog Kf (♦)--Dog Br (▽)--Dog Bn

(■)--Mean coordinates in Greyhounds

TABLE 4
RESULTS IN GREYHOUNDS

Dog	Mapping technique ^a	Coordinates ^b		Distance between coordinates (in mm) ^c
		AP axis	ML axis	
Kf	A	16.9	5.5	AL=6.6
	L	17.7	12.1	HL=4.3
	H	14.9	8.9	HA=3.9
Br	A	15.2	8.9	AL=2.5
	L	13.9	6.8	HL=0.5
	H	13.6	7.2	HA=2.3
Bn	A	14.2	7.7	AL=3.8
	L	15.3	9.3	HL=3.4
	H	18.6	9.9	HA=4.9
Mean ^d	A	15.4 ±0.8	7.4 ±1.0	AL=4.3 ±1.2
	L	15.6 ±1.1	9.4 ±1.5	HL=2.7 ±1.1
	H	15.7 ±1.5	8.7 ±0.8	HA=3.7 ±0.8

^aMapping technique used:

A--Analysis of RMS amplitude of signal

L--Analysis of latency of signal

H--Analysis of histological data

^bCoordinates (in mm) along the anterior-posterior (AP) and medial-lateral (ML) axes. All of the coordinates given are lateral to the midline and anterior to the IAP.

^cDistance between the areas of central vision as determined by:

AL--the RMS amplitude and the latency of the signal

HL--histology and the latency of the signal

HA--histology and the RMS amplitude of the signal

^dMean coordinates ± one standard deviation.

anterior-posterior axis ($p=0.99$) nor at the medial-lateral axis ($p=0.59$).

A second method of analysis was to calculate the distances between the three sets of coordinates obtained in each dog, i.e., the lengths of the three sides of the triangle described by these coordinates (Figure 9). Results of these calculations are presented in the last column of Table 4. In no case were two coordinates in a given dog more than 6.6 mm

apart, and the mean distance between any two coordinates was 3.6 mm. Multiple Student's t-tests yielded no significant differences between the three sets of distances calculated ($p>0.40$). An ANOVA test revealed no significant differences between the three mean distances ($p=0.27$), implying that the triangle described by the three mean coordinates is statistically equilateral.

Based on the overall mean of the coordinates obtained by all three mapping techniques, it was determined that the cortical area of central vision in Greyhounds lies 15.6 ± 0.1 mm anterior to the IAP and 8.5 ± 0.6 mm lateral to the midline.

Comparison of the Three Experimental Groups

Normal and Pre-glaucomatous Beagles

Results of the three mapping techniques (i.e., analysis of RMS amplitude, latency and histology) were compared in normal and pre-glaucomatous Beagles. Using the Student's t-test, there were no significant differences in the location of the cortical area of central vision between the two groups, at neither the anterior-posterior axis ($p=0.72$, $p=0.80$ and $p=0.67$, respectively) nor at the medial-lateral axis ($p=0.84$, $p=0.54$ and $p=0.69$, respectively). Based on these results, it was determined that the cortical area of central vision in Beagles lies 11.3 ± 0.4 mm anterior to the IAP, and 8.3 ± 0.1 mm lateral to the midline.

The location of the cortical area of central vision in Beagles is presented in Figures 10 and 11. Figure 10 is a potential map showing the distribution of the mean signals' RMS amplitudes recorded from the cortical surfaces of nine Beagles. The decrease in signal amplitude as one moves away from the cortical area of central vision can be appreciated (see also Figure 5). Figure 11 is a latency map showing the distribution of the mean signals latencies recorded from the cortical surfaces of nine Beagles. The increase in signal latency as one moves away from the cortical area of central vision can be appreciated (see also Figure 5).

Figure 12 presents the rate of change in the mean signal's RMS amplitude and latency in nine Beagles as the electrode was moved from the cortical area of central vision along the anterior-posterior and medial-lateral axes. Since simultaneous PERG recordings did not alter significantly during the experiments, changes seen in the PVEP amplitude and latency can only be due to changes in the cortical recording site.

Beagles and Greyhounds

No significant differences in the location of the cortical area of central vision along the medial-lateral axis were found between normal Beagles and Greyhounds ($p=0.58$, $p=0.48$ and $p=0.96$, respectively). Nor were any such differences

Figure 10.

The distribution of the mean signal RMS amplitudes in Beagles.

a) A coordinates map. Lines mark the coordinates of the mean recording sites in nine Beagles.

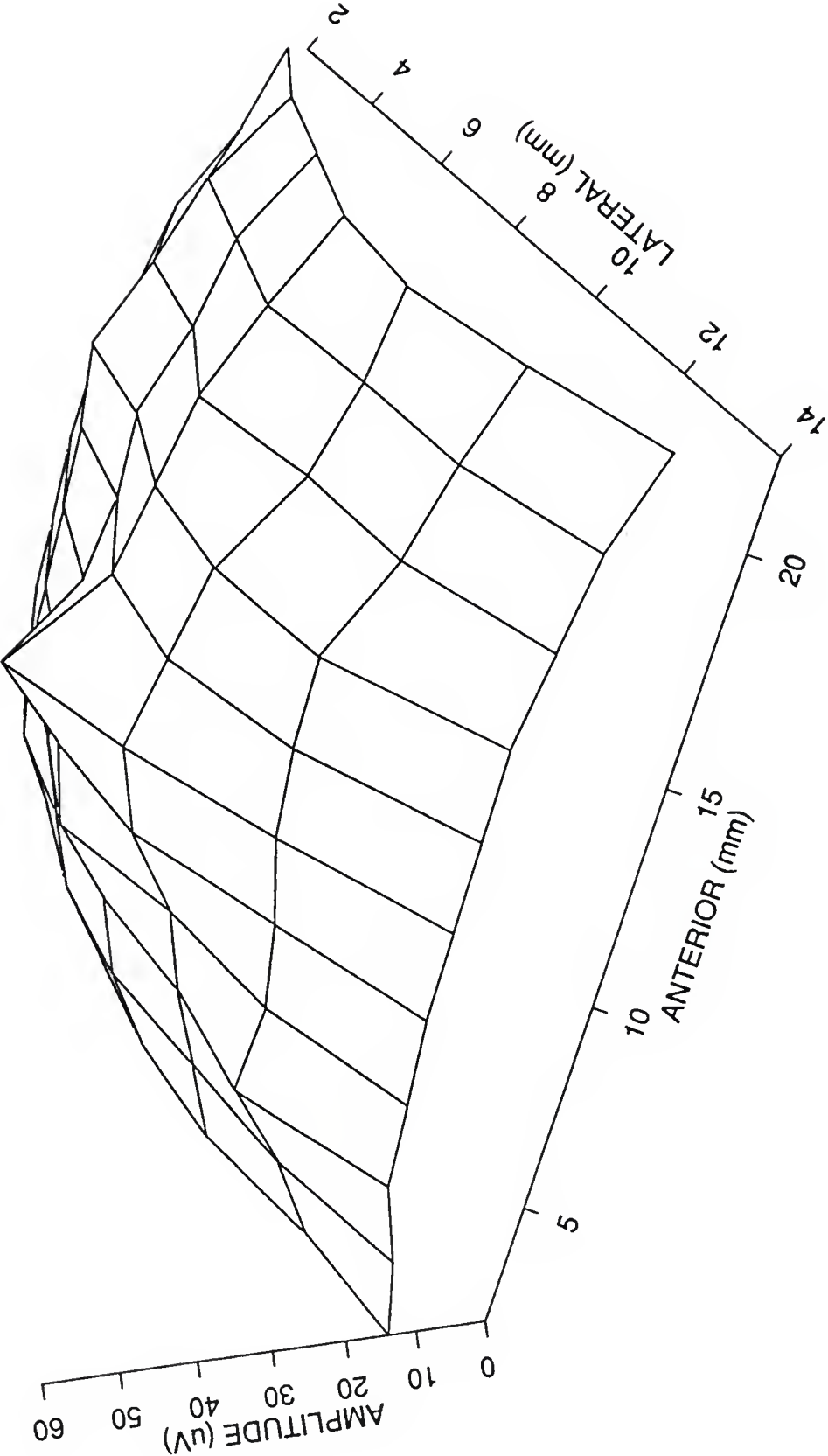
Anterior axis--distance, in mm, anterior to the IAP.

Lateral axis--distance, in mm, lateral to the midline.

Vertical axis--mean RMS amplitude of the recorded signal, in μV .

The cortical area of central vision was determined by the highest mean RMS amplitude recorded ($63 \mu V$). It is located 11.7 ± 0.8 mm anterior to IAP and 8.4 ± 0.8 mm lateral to the midline.

b) An isopotential map. The map shows the distribution of mean signal RMS amplitude in nine Beagles, as a function of the change in amplitude. Axes labelling and signal coordinates are the same as in figure 10a.



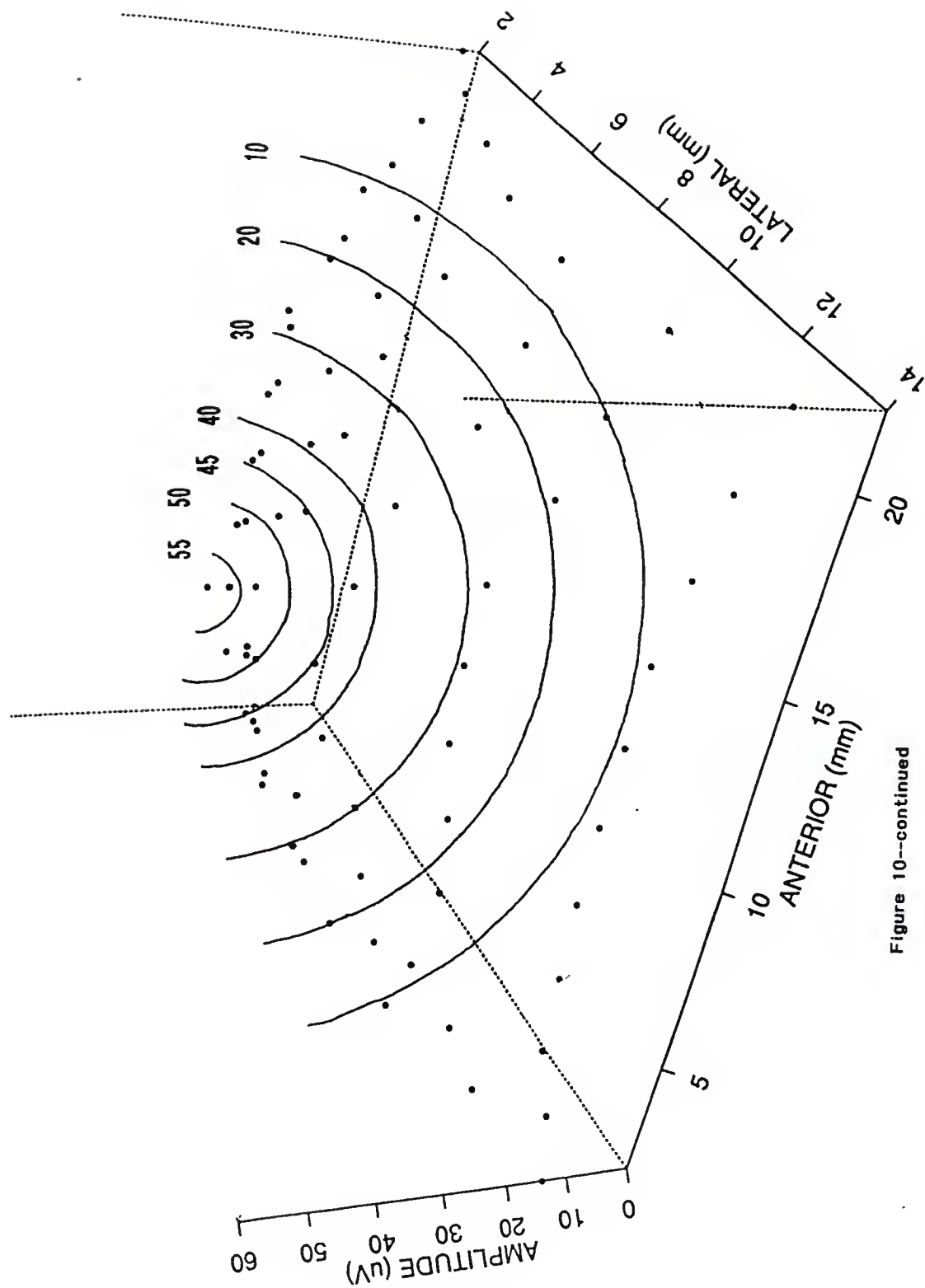


Figure 10--continued

Figure 11.

The distribution of the mean signal latencies in Beagles.

a) A coordinates map. Lines mark the coordinates of the mean recording sites in nine Beagles.

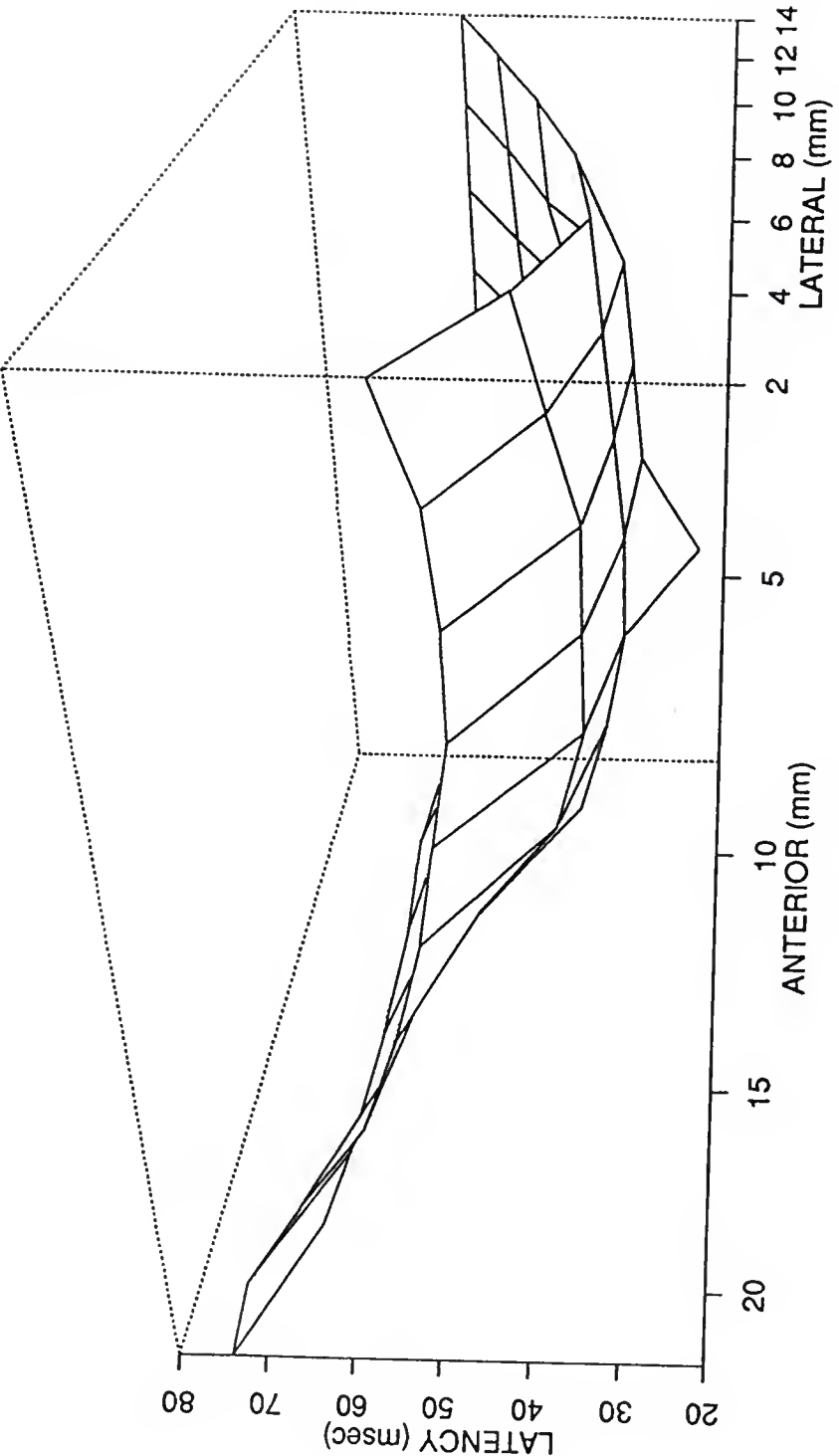
Anterior axis--distance, in mm, anterior to the IAP.

Lateral axis--distance, in mm, lateral to the midline.

Vertical axis--mean latency of the recorded signal, in msec.

The cortical area of central vision was determined by the shortest mean latency recorded (23 msec). It is located 9.8 ± 0.8 mm anterior to IAP and 7.6 ± 0.9 mm lateral to the midline.

b) An isolatency map. Map shows the distribution of mean signal latency in nine Beagles. Each expanding rectangle denotes an increase of 10 msec in the latency of the mean signal recorded at these coordinates. Axes labelling and signal coordinates are the same as in Figure 11a.



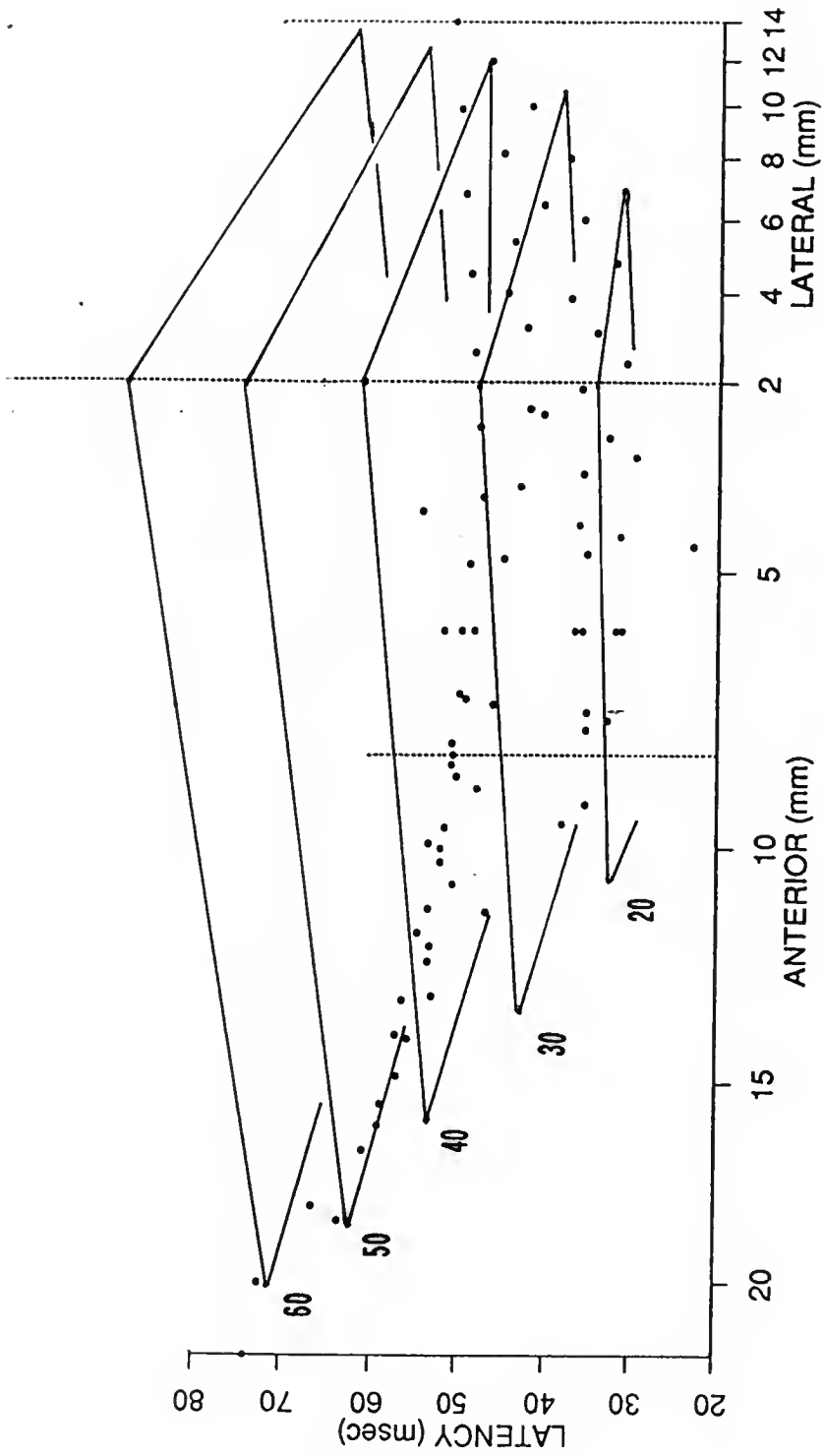


Figure 11--continued

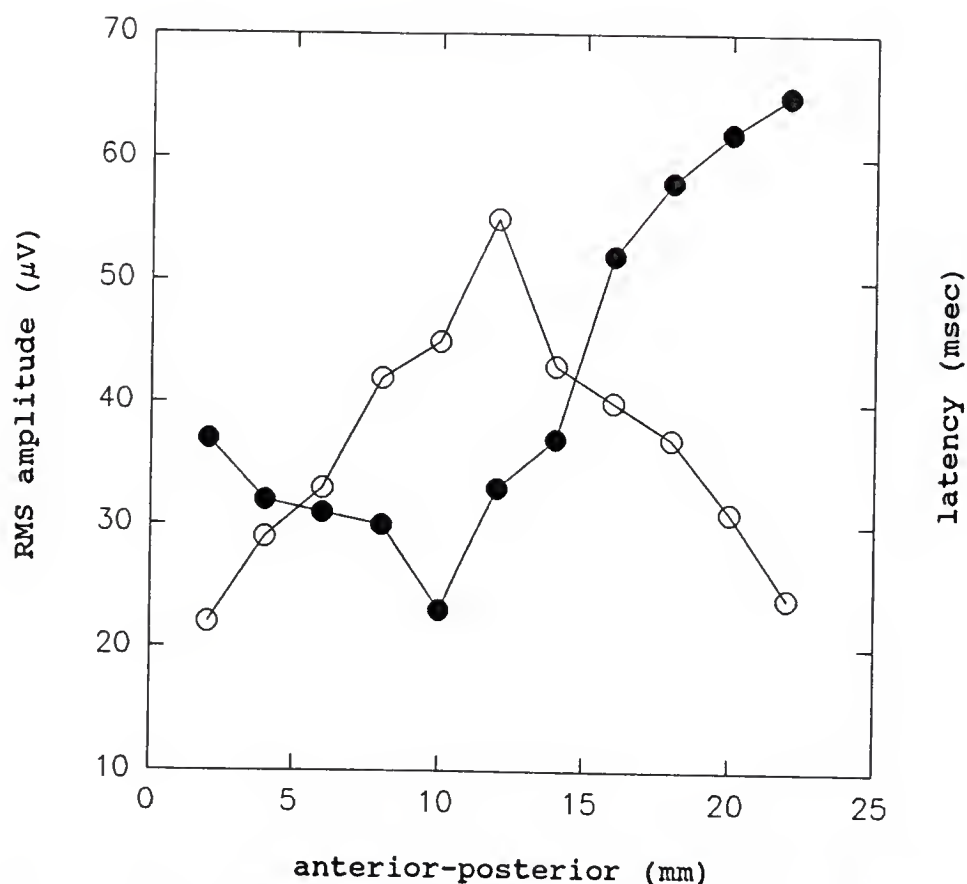


Figure 12. Rate of change in mean signal RMS amplitude and latency in Beagles.

a) Rate of change in mean signal RMS amplitude and latency along the anterior-posterior axis in nine Beagles.

(O) Root mean square amplitude of mean signal (in μV). Stereotaxic coordinates along the anterior-posterior axis are shown on the X-axis. Medial-lateral coordinates were 8.3 mm.

(●) Latency of mean signal (in msec). Stereotaxic coordinates along the anterior-posterior axis are shown on the X-axis. Medial-lateral coordinates were 8.3 mm.

b) Rate of change in signal RMS amplitude and latency along the medial-lateral axis.

(O) Root mean square amplitude of mean signal (in μV). Stereotaxic coordinates along the medial-lateral axis are shown on the X-axis. Anterior-posterior coordinates were 11.3 mm.

(●) Latency of mean signal (in msec). Stereotaxic coordinates along the medial-lateral axis are shown on the X-axis. Anterior-posterior coordinates were 11.3 mm.

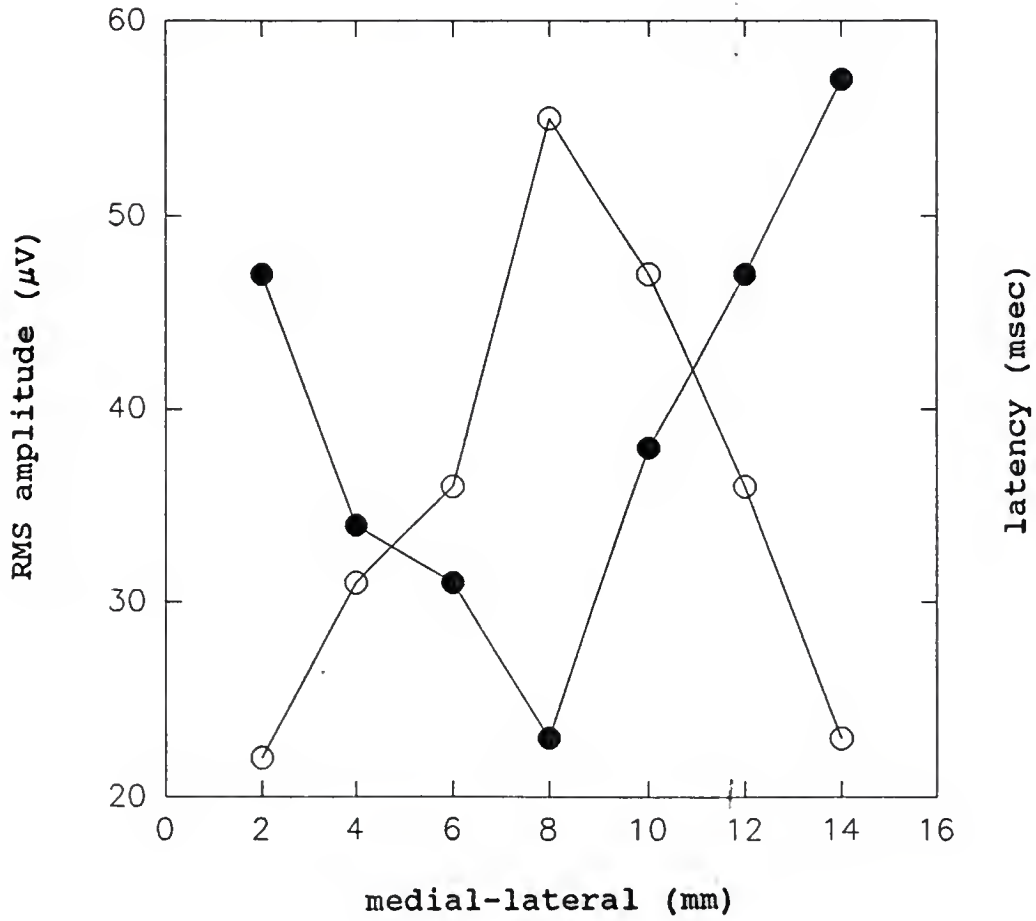


Figure 12--continued

found between pre-glaucomatous Beagles and Greyhounds ($p=0.48$, $p=0.28$ and $p=0.71$) respectively. In other words, no inter-breed differences were found in the location of the cortical area of central vision along the medial-lateral axis.

All three mapping techniques showed significant differences in the location of the cortical area of central vision along the anterior-posterior axis between normal Beagles and Greyhounds ($p=0.04$, $p=0.005$ and $p=0.04$ respectively). However, none of the mapping techniques revealed such differences between pre-glaucomatous Beagles and Greyhounds ($p=0.09$, $p=0.10$ and $p=0.20$, respectively).

Comparison of the Three Mapping Techniques

Accuracy of the Three Mapping Techniques

A χ^2 test of observed and expected frequencies was performed to test the hypothesis that no one mapping technique yielded consistently more accurate results than the other two techniques. If the hypothesis is false and one technique yields more accurate results, the coordinates obtained by that technique would consistently be closest to the mean coordinates of the experimental group. However, if the hypothesis is true and no differences exist between the mapping techniques, each technique would be expected to prove most (and, conversely, least) accurate in four of the 12 dogs tested. The observed and expected frequencies of the number of times each technique yielded the most accurate results in the

anterior-posterior and medial-lateral axes are given in Table 5 and Table 6, respectively.

The result of the test for the anterior-posterior axis was $\chi^2=0.5$. The result of the test for the medial-lateral axis was $\chi^2=3.4$. Based on these results it was determined (at a confidence level of $\alpha=5\%$) that at neither axes was one mapping technique superior to the other two techniques.

TABLE 5
EXPECTED AND OBSERVED FREQUENCIES
OF ACCURACY IN THE ANTERIOR-POSTERIOR AXIS

	Amplitude of signal	Latency of signal	Histology	Total
Expected	4	4	4	12
Observed	4	3	5	12

TABLE 6
EXPECTED AND OBSERVED FREQUENCIES
OF ACCURACY IN THE MEDIAL-LATERAL AXIS

	Amplitude of signal	Latency of signal	Histology	Total
Expected	4	4	4	12
Observed	2.5	2.5	7	12

Linkage Between the Three Mapping Techniques

It has already been stated that ANOVA and multiple Student's t-tests failed to reveal any significant differences in the distances between the three sets of coordinates obtained for a given dog at any of the experimental groups. This finding implies that no two given mapping techniques

yielded consistently similar results. Had there been such a pair of mapping techniques, the distance between the coordinates obtained by those techniques would have consistently been the shortest of the three calculated distances.

A χ^2 test of observed and expected frequencies was also conducted to further check the degree of linkage between the three tests. If no two given mapping techniques yielded consistently similar results, the distance between the coordinates obtained by those two techniques would be the shortest (and, conversely, the longest) in four out of the 12 dogs. The observed and expected number of times in which a distance was the shortest of the three measured distances in a given dog are shown in Table 7.

TABLE 7
EXPECTED AND OBSERVED FREQUENCIES
OF SHORTEST DISTANCES

	AL	HL	HA	TOTAL
Expected	4	4	4	12
Observed	5	4	3	12

The result of the test was $\chi^2=0.5$. Therefore, it was determined (at a confidence level of $\alpha=5\%$) that no two tests possessed an unusually high degree of linkage.

The Canine AMF

The AMF for the cortical area of central vision was determined by calculating the area where a signal which was at least 37% of the maximal signal could be recorded. The 37% threshold, equivalent to a 63% drop in the maximal signal, was chosen because it represents the distance along which extrapolar electronic potential decays to $1/e$ (natural logarithm) of its original level (141). This value, known as the space constant, or λ , is used extensively in neurophysiology to calculate signal amplitude at a given distance from the generating source of the action potential (141).

Based on this threshold value and on the RMS amplitude of the mean signal recorded in Beagles (Figure 10), it was determined that on the cortical surface, the canine area of central vision is described by a circle with a radius of 12.2 mm. In other words, 468 mm² of cortex are devoted to representation of the central 15° of vision. Therefore, the mean AMF for the central 15° of vision in the dog is 2.6 mm²/degree² of visual field.

CHAPTER 4 DISCUSSION

The Cortical Area of Central Vision in the Dog

Location of the Area of Central Vision on the Surface of the Canine Cortex

Based on the results of this study, it was determined that the cortical area of central vision in Beagles lies 11.3 ± 0.4 mm anterior to the IAP, and 8.3 ± 0.1 mm lateral to the midline (see Figures 10 and 11). In Greyhounds the cortical area of central vision lies 15.6 ± 0.1 mm anterior to the IAP and 8.5 ± 0.6 mm lateral to the midline. Anatomically, the canine area of central vision in both breeds is located near the medial border of the posterior occipital lobe, at the junction of the marginal and endomarginal gyri (see Figures 13 and 14).

Glaucoma and the Location of the Area of Central Vision

No significant differences in the location of the cortical area of central vision were found between normal and pre-glaucomatous Beagles ($p > 0.54$). This finding may be due to the small sample ($n=2$) of glaucomatous Beagles used in the study, but it is more likely that in mature dogs primary glaucoma has no effect whatsoever on the location of the

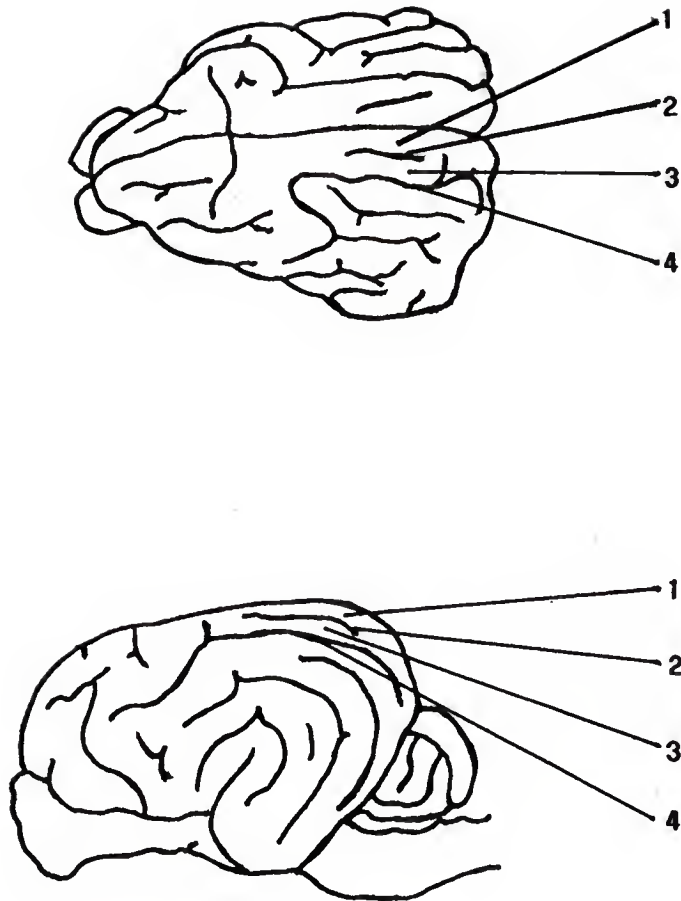


Figure 13. A diagram of the canine cerebral cortex.

Top-a left dorsolateral view.

Bottom-a lateral view.

(1) endomarginal gyrus; (2) endomarginal sulcus;
(3) marginal gyrus; (4) marginal sulcus.

From: Evans HE, Christensen GC (Eds). Miller's Anatomy of the Dog. WB Saunders Co., Philadelphia (2nd edition) 1979 (ref #142).

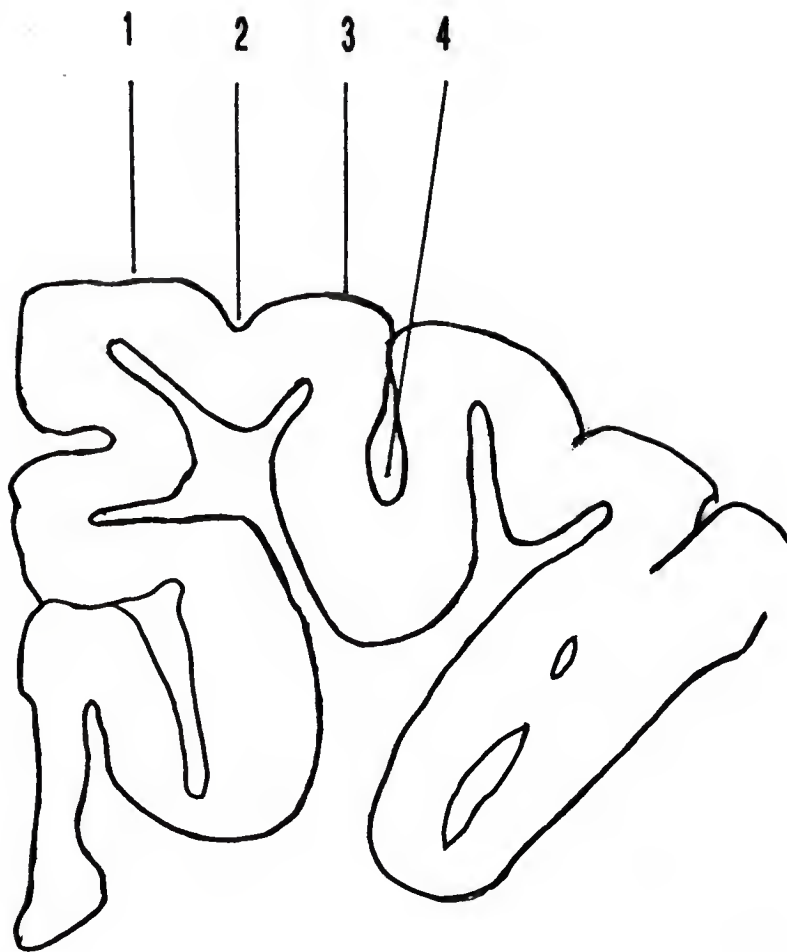


Figure 14. A representation of the canine medial occipital lobe in the dog (transverse section).
(1) endomarginal gyrus; (2) endomarginal sulcus;
(3) marginal gyrus; (4) marginal sulcus.

From: Yoshikawa T. Atlas of the Brains of Domestic Animals.
University of Tokyo Press, Tokyo, 1968 (ref #143).

cortical area of central vision. A careful search of the literature failed to reveal a report of such an effect in any species. While primary glaucoma is known to affect VEP recordings in glaucomatous humans and in nonhuman primates with experimentally induced IOP elevation (105-113), this is most likely due to the effect of the elevated pressure on the retina and the optic nerve rather than to a direct effect on the visual cortex itself.

Numerous studies, including landmark works by Hubel and Wiesel, have shown that visual deprivation at a young age can permanently disrupt the neuronal organization of the visual cortex in nonhuman primates and other species (32, 144). However, by age 6 weeks in nonhuman primates (32), and age 8 weeks in cats (144) the visual cortex completes its development, and visual deprivation has no effect on its neuronal organization. While no similar data exists in dogs, it has been shown that the canine visual cortex assumes the morphological characteristics of an adult cortex by age 4 weeks (145), and that canine VEP's reach adult levels by age 100 days (53). The pre-glaucomatous dogs used in these experiments were from a colony of Beagles with hereditary POAG in which visual losses resulting from the disease occur at a much later age (119). It is conceivable that congenital glaucoma in dogs (and other species) would disrupt the neuronal organization of the visual cortex. But it is extremely hard to imagine such a disruption occurring when the

onset of the clinical disease is long after the cortex has completed its physiological and morphological development, at an age when even full deprivation has no effect in other species (32, 144). This line of reasoning, together with the lack of significant differences in the results of glaucomatous and normal Beagles, led to the pooling of the results of the two experimental Beagle groups.

Comparison of Results in Beagles and Greyhounds

No significant differences in the location of the cortical area of central vision were found between Beagles and Greyhounds in the medial-lateral axis ($p>0.28$). However significant differences in the location of the cortical area of central vision between the two breeds were found along the anterior-posterior axis ($p=0.04$). Unfortunately, no comparative study of the Beagle and Greyhound brain has been conducted at neither the histological nor the macroscopic level (Drs. C. Chrisman, F. Thompson and R. Reep, personal communications). Therefore it cannot be determined if the variation in the location of the cortical area of central vision found between the two breeds is a result of differences in brain sizes or the result of evolutionary divergence in two canine breeds bred for different tasks.

It has been shown that the latency of BAEP's in the dog is correlated with body weight and with cranium distance (which reflects the cranium length and width). An increase of

1 cm in cranium distance can increase the canine BAEP latency by up to 0.03 msec, while an increase of 1 kg in body weight can increase the latency by up to 0.01 msec (146). It has been estimated that head size, which accurately reflects brain size, is a source of 25% of intersubject variance in the latency of the canine BAEP (146). No data exists on the effect of head and brain size on canine VEP's, but in humans brain size has been shown to affect the latency of the P100 (147). These facts, combined with the similarity in the anatomical (as opposed to the stereotaxic) location of the cortical area of central vision in Beagles and Greyhounds tend to support the hypothesis that differences between the two breeds are a result of differences in head and brain size.

Histological Location of the Cortical Area of Central Vision

No significant differences were found between the cortical areas of central of vision in Beagles ($p>0.18$) and in Greyhounds ($p>0.30$) as determined by electrophysiology and histology. In fact, in both breeds, there was a remarkable degree of correlation between the electrophysiological and histological findings. This finding is also consistent with results of investigations of all species mapped to date, showing the electrophysiologically-determined cortical area of central vision to be invariably located at the junction of Brodmann's areas 17 and 18 (3, 4, 7, 8, 11, 13, 17, 20, 26).

Several researchers have conducted histological studies of the canine brain (148-151). Early maps divide the canine occipital cortex into three cytoarchitectonically-defined areas, which, based on Brodmann's nomenclature, have been designated 17a, 17b and 18 (149, 150). Based on this terminology, the cortical area of central vision lies at the border of areas 17a and 17b. More recently, it has been proposed that the canine occipital cortex is divided into six cytoarchitectonically-defined areas (151). Based on this terminology, the cortical area of central vision lies at the border of areas M and Emr. Another study, based on the myeloarchitecture of the region, suggests there are 15 morphologically-defined areas in the canine occipital cortex (148). The three largest areas have been designated MP, BP and QP (148), and the cortical area of central vision lies at the border of areas MP and BP. It remains to be determined whether, as in other species, the division of the canine occipital cortex into several morphologically-defined areas can be correlated with the existence of multiple visual maps and higher processing centers.

Comparison to the Cat

The only other carnivore whose visual cortex has been mapped to date is the cat (2). The stereotaxic coordinates of the cortical area of central vision in the cat are 3 mm

posterior to the IAP and 5 mm lateral to the midline (see Figure 2) (40). Based on the results of this study, the cortical areas of central vision in the cat and the Beagle are 14.7 mm apart. In the cat and the Greyhound, the distance is even further, 18.9 mm.

There is a much smaller difference in the anatomical location of the cortical area of central vision between the two species, if at all. In both carnivores, the cortical area of central vision is located near the medial border of the posterior occipital lobe. More specifically, it is located on the crown of the lateral gyrus, near the junction of the lateral and posterior lateral gyri in the cat (20). In the dog, it is located at the junction of the marginal and endomarginal gyri (see Figures 13 and 14). Studies that compared the fissural pattern of the canine and feline brains report that the marginal gyrus of the dog is homologous to the lateral gyrus of the cat (152, 153). Indeed, at least two textbooks refer to the marginal gyrus of the dog as the "lateral gyrus" (118, 120), and one textbook refers to the lateral gyrus of the cat as the "marginal gyrus" (154).

Once again, it remains to be determined whether the difference in the location of the cortical area of central vision in the dog and the cat is the result of difference in brain size or the result of evolutionary changes. In other words, has evolution in the dog consisted simply of increased elaboration of the same parts already established in the

common ancestors of carnivores, or have new parts evolved? The question has already been posed by vision researchers (17), and obviously a definitive answer cannot be provided without finding the common carnivore ancestor.

As in the comparison of the Beagle and the Greyhound, the similarity in anatomical, as opposed to stereotaxic, location, lends support to the former hypothesis. A second clue may be found by comparing the AMF of the cat and the dog. A larger cortical area is devoted to representation of the central visual area in the dog brain, as compared to the cat brain. In the mid-sized dog, 468 mm² of cortex are devoted to representation of the central 15° of vision, while in the cat the respective figures are 190 mm² and 20° (20).

It has already been established by Tusa et al. that in the cat AMF values decrease linearly along both the horizontal and vertical meridians (20, 39). The same assumption has been used by Whitteridge in calculating the AMF in nonhuman primates (35). If the same principle holds true for the dog, then the AMF for the central 1° of vision in the dog is 3.85 mm² of cortex/degree² of visual field. In the cat, the peak AMF value is 3.6 mm² of cortex/degree² of visual field (20).

The AMF is directly related to cone density, ganglion cell concentration and visual resolution both in nonhuman primates (35, 155) and in humans (156). Consequently, the relationship of AMF to the number and concentration of ganglion cells indicates a precise, and similar, topographical

arrangement of the visual pathways in nonhuman primates (35, 155) and in humans (156). The relationship between AMF and the cone density indicates a similar arrangement of retinal organization in these species (35, 155, 156). In humans it has been shown that both cone and ganglion cell distributions are related to image resolution, color perception and other important basic visual functions (156).

As Table 8 shows, the same principles hold true in carnivores. It would seem that cats and dogs share similar topographical arrangement of their retina and visual pathways. Furthermore, it seems that these two carnivores share similar principles of organization with nonhuman primates and humans, a finding that may help shed light on the evolution of vision in these divergent species.

TABLE 8
RETINAL CELL COUNTS
AND VISUAL FUNCTION

Species	AMF mm ² /degree ²	Maximal cone density/mm ²	number of ganglion cells	resolution (cpd)
cat	3.6 ⁽²⁰⁾	27,000 ⁽¹⁵⁷⁾	116,000 ⁽¹⁵⁸⁾	3.5 ⁽¹⁵⁹⁾
dog	3.9 ^a	102,000 ⁽¹⁴⁰⁾	167,000 ⁽¹⁶⁰⁾	4.3 ⁽¹⁰²⁾
rhesus	5.5 ⁽¹⁵⁵⁾	148,000 ⁽¹⁵⁵⁾	1.0x10 ⁶ ⁽¹⁶¹⁾	46 ⁽¹⁵⁵⁾
man	11.6 ⁽¹⁶²⁾	260,000 ⁽¹⁶³⁾	1.3x10 ⁶ ⁽¹⁶⁴⁾	60 ⁽¹⁶⁵⁾

^athis study

The Recorded Signal

Several hypotheses can be used to explain the changes in signal RMS amplitude and latency as the electrode was moved away from the cortical area of central vision (see Figure 12). It is possible that the observed decrease in RMS amplitude is due to "volume conduction", the decay observed in any electrical signal as one moves away from its source. However, such a decay would be constant (and proportional to $1/\text{distance}^2$) in all directions, and it is obvious by comparing Figures 12a and 12b that the rate of decrease in RMS amplitude was not the same along both axes. Furthermore, had the change in signal RMS amplitude been due to volume conduction only, one would not expect to see it accompanied by a concomitant increase in latency. Conduction over the distances involved should be instant.

Obviously, physiological decay in signal RMS amplitude due to volume conduction occurs in the canine cortex. However, it alone cannot account for the observed changes in the recorded RMS amplitude and latency. These changes can only be explained if the existence of other cortical visual areas is hypothesized. As stated previously, it is more than likely, based on findings in all other mammalian species and on the histological divisions of the canine occipital cortex, that the dog has more than one cortical visual area. Furthermore,

it has been established in both the cat (43) and in nonhuman primates (68) that the area centralis/macula is not equally represented in all of the cortical visual areas. In other words, in some visual areas of these species the central retina is hardly represented (has a low AMF value). Therefore, stimulation of the area centralis/macula would not result in significant biological activity in these cortical areas. It is very likely that similar organization exists in the dog, and as the electrode was moved into these regions less neuronal activity was recorded. This hypothesis would also explain the observed increase in signal latency, since visual input from the primary visual cortex to these areas would involve one or more synapses.

Significance of this Study

The location of the visual cortex in man has been known for more than 70 years (1). The cat's visual cortex was mapped 50 years ago (2). In both these species, knowing the precise location of the visual cortex and the area of central vision has proven to be a vital piece of information for both researchers and clinicians. This knowledge is essential for our understanding of the evolution, organization and function of both the visual system and the brain. Knowledge of the accurate location of the primary visual cortex is also valuable in diagnosis and therapy of cerebral disorders, trauma and neoplasia, and performing effective neurosurgery

(166-168). Accurate visual-evoked potentials (VEP) recordings can only be carried out if one knows precisely where to place the electrodes (23). Displacing the active cortical electrode by as little as 5 mm can cause a decrease of up to 25% (depending on the spatial frequency of the stimulus) in the amplitude of the canine VEP (Dawson, personal observations). In humans it has been reported that a 2.5 cm displacement of the active electrode can cause a 75% decrease in the amplitude of the VEP (100).

Recordings of VEP have numerous clinical and research applications. In humans they are used to evaluate visual function and to determine visual acuity in patients suffering from cataracts, corneal opacities and astigmatism (166). They are also used to help determine the diagnosis and prognosis, and to monitor the treatment, of people suffering from demyelinating neural diseases, retrobulbar neuritis, multiple sclerosis, progressive neurometabolic storage diseases, photosensitive epilepsy and strabismic amblyopia (167, 168). Since VEP recordings do not require voluntary participation of the patient, they are especially useful to clinicians treating infants, elderly and mentally handicapped people, and by analogy, in animals, which also may be afflicted by all of the above-mentioned diseases (166-168).

Despite the fact that VEP recordings are routinely performed in humans, their clinical use in animals has been severely limited by the lack of knowledge of the specific

location of the primary visual cortex. Electrophysiological visual research in animals has also been hampered for the same reason. One researcher stated that "the VEP hasn't been a fully exploited diagnostic technique in animals" (169). Another notes that "VEP recording in animals with scalp electrodes was unsuccessful" (130). It is obvious that one basic problem facing these researchers and clinicians is that the area of central vision in the dog, the species most frequently seen in veterinary ophthalmology clinics, has never been mapped. Standard veterinary ophthalmology and neurology textbooks either make no reference to the location of the canine visual cortex (170), refer to it simply as the occipital lobe (171, 172), or discuss its location in the cat and nonhuman primates (74, 173).

Mapping of the area of central vision in the canine cortex is essential for standardization of canine VEP recordings (174), since misplacement of electrodes is a major source of VEP variation (23). Indeed, researchers performing VEP recordings in dogs often used data obtained from cats when placing their electrodes (175). As it turns out, such practices lead, in the case of Greyhounds, to a 19 mm deviation from the correct electrode position. Obviously, such improvisation casts doubt on the reliability of any results obtained. It also severely limits the use of the dog, which has already proven to be a successful animal model for some human ophthalmological disorders in research (176). A VEP

recording protocol, including instructions for electrode placement, has already been published for use in the cat (60). The aim of this study was to locate and map the area of central vision in the dog, so that a similar VEP protocol can be produced for the dog. A great gap in the understanding of the canine visual system and brain has thus been filled.

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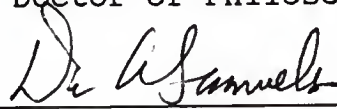
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BIOGRAPHICAL SKETCH

Ron Ofri was born on May 11th, 1960, in Tel Aviv, Israel. He grew up in Israel, except for a 4-year period when the family moved to Tokyo, Japan, where his father served with the Israeli Embassy. Following a 3-year service in the Israeli army and a year of travelling in Asia, Ron started attending the Hebrew University of Jerusalem. He obtained his B.Sc. in biology in 1985, and went on to become a member of the charter class of the Koret Veterinary School of the Hebrew University of Jerusalem. After receiving his DVM degree in 1989 he moved to Gainesville, FL, where he received his Ph.D. for work on canine visual electrophysiology at the University of Florida. Upon completion of his studies in the USA, Ron plans to return to Israel and join the faculty of the Koret Veterinary School.

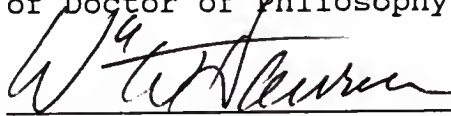
Ron is married to Iris, and the couple has 2 children, Anat and Jonathan. Both children were born during the course of Ron's studies at the University of Florida.

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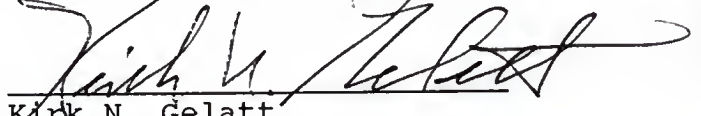
Don A. Samuelson, Chair
Associate Professor of
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William W. Dawson
Professor of Neuroscience

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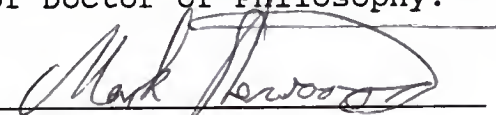
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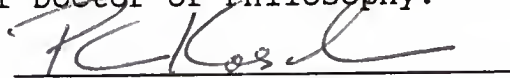
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This dissertation was submitted to the Graduate Faculty of the College of Veterinary Medicine and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 1993



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